U.S. Army Center for Health Promotion and Preventive Medicine

USCHPPM

ACUTE TOXICITY ESTIMATION AND OPERATIONAL RISK MANAGEMENT OF CHEMICAL WARFARE AGENT EXPOSURES

USACHPPM REPORT NO. 47-EM-5863-04

MAY 2004

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U.S. ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE

The U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) lineage can be traced back over 50 years to the Army Industrial Hygiene Laboratory. That organization was established at the beginning of World War II and was under the direct jurisdiction of The Army Surgeon General. It was originally located at the Johns Hopkins School of Hygiene and Public Health, with a staff of three and an annual budget not to exceed $3000. Its mission was to conduct occupational health surveys of Army operated industrial plants, arsenals, and depots. These surveys were aimed at identifying and eliminating occupational health hazards within the Department of Defense's (DOD) industrial production base and proved to be beneficial to the Nation's war effort.

Until 1995, it was nationally and internationally known as the U.S. Army Environmental Hygiene Agency or AEHA. Its mission is expanding to support the worldwide preventive medicine programs of the Army, DOD and other Federal Agencies through consultations/ supportive services; investigations and training.

Today, AEHA is redesignated the U.S. Army Center for Health Promotion and Preventive Medicine. Its mission for the future is to provide worldwide technical support for implementing preventive medicine, public health and health promotion/wellness services into all aspects of America's Army and the Army Community anticipating and rapidly responding to operational needs and adaptable to a changing work environment.

The professional disciplines represented at the Center include chemists, physicists, engineers, physicians, optometrists, audiologists, nurses, industrial hygienists, toxicologists, entomologists, and many other as well as sub-specialties within these professions.

The organization's quest has always been one of excellence and continuous quality improvement; and today its vision, to be the nationally recognized Center for Health Promotion and Preventive Medicine, is clearer than ever. To achieve that end, it holds ever fast to its values which are steeped in its rich heritage:

- *Integrity is the foundation*
- *Excellence is the standard*
- *Customer satisfaction is the focus*
- *Its people are the most valued resource*
- *Continuous quality improvement is its pathway*

The organization, which stands on the threshold of even greater challenges and responsibilities, has General Officer leadership. As it moves into the next century, new programs are being added related to health promotion/wellness, soldier fitness and disease surveillance. As always, its mission focus is centered upon the Army Imperatives so that we are trained and ready to enhance the Army's readiness for war and operations other than war.

It is an organization fiercely proud of its history, yet equally excited about the future. It is destined to continue its development as a world-class organization with expanded services to the Army, DOD, other Federal Agencies, the Nation and the World Community.

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DEPARTMENT OF THE ARMY
US ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE
5158 BLACKHAWK ROAD
ABERDEEN PROVING GROUND MD 21010-5403

REPLY TO
ATTENTION OF

EXECUTIVE SUMMARY

ACUTE TOXICITY ESTIMATION AND OPERATIONAL RISK MANAGEMENT OF CHEMICAL WARFARE AGENT EXPOSURES
USACHPPM REPORT NO. 47-EM-5863-04
MAY 2004

1. PURPOSE. To address a broad range of related issues associated with chemical risk assessment and operational risk decision making. While this report focuses on a specific group of chemical warfare agents (GA, GB, GD, GF, VX and HD) and exposure routes (i.e., inhalation, ocular, percutaneous), the concepts and recommendations extend to other chemicals (i.e., other warfare agents and toxic industrial chemicals (TICs)) as well as other exposure routes (i.e., ingestion). The guidance and recommendations address a variety of questions that have been asked of the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) over the past several years by operational, medical, and research/acquisition audiences. The concepts and recommendations in this report are also being used by USACHPPM to update previous guidance put forth in USACHPPM Technical Guide 230, *Chemical Exposure Guidelines for Deployed Military Personnel.*

This report's primary objective is to provide implementing guidance and recommendations pertaining to the use and interpretation of the December 2001 Deputy Assistant to The Secretary of Defense Chemical and Biological (Warfare Agent) Defense ((DATSD-CBD) interim-certified acute toxicity values for the chemical warfare agents (CWA) GA, GB, GD, GF, VX and HD. Specifically, this report—

a. Demonstrates how the interim-certified acute toxicity values can be effectively incorporated into Army/Joint Service Operational Risk Management (ORM) terminology as required by Joint Staff guidance on Force Health Protection (FHP) and environmental health surveillance.

b. Demonstrates how users can select, extrapolate, and adjust toxicity criteria from the set of DATSD-CBD interim-certified acute toxicity estimates to address various questions (to include "what is low-level exposure?").

c. Provides specific objectives to address a variety of chemical defense measures (e.g., such as modeling and simulation/planning and prediction, contamination avoidance (detection), protection, decontamination, and medical intervention.

d. Compares the DATSD-CBD interim-certified acute toxicity values with existing acute civilian toxicity guidelines to help address the potential overlap of military and Homeland Security measures for chemical defense.

2. CONCLUSIONS AND RECOMMENDATIONS.

a. Translating Toxicity Information into ORM Terminology.

The 2001 DATSD-CBD toxicity criteria provide a range of values that should be interpreted according to existing military ORM hazard severity categories (i.e., Catastrophic, Critical, Marginal, Negligible). This will ensure consistent risk management decision making and accommodate current FHP requirements. Since doctrinal definitions of hazard severity and risk levels have not historically been tied to toxicity levels, a standard description of the types of health impacts associated with the different ORM hazard severity categories is necessary. USACHPPM provides the following hazard severity health impact descriptions to apply to any type of military chemical hazard assessment (i.e., chemical warfare or TICs). Section 2 of this report describes how these definitions accommodate existing ORM risk definitions and established unit degradation criteria**.** Section 5.0 and Table 5.1 describe the toxicity estimate criteria that correspond to each hazard severity category.

- Health Impacts Associated with Catastrophic Hazard Severity: Increasing deaths and casualties with severe disabling/incapacitating effects requiring significant medical attention (e.g., Echelon IV) and/or additional personnel support for survival.

- Health Impacts Associated with Critical Hazard Severity: Few, if any deaths, but significant numbers of disabling/incapacitating casualties, many requiring medical treatment or support (e.g., minimum Echelon III, possibly Echelon IV); others are likely to have noticeable but not disabling health effects.

- Health Impacts Associated with Marginal Hazard Severity: Many persons may have noticeable but not disabling health effects; the potential for individuals to have reversible, delayed (post-mission or deployment) health effects is considered very possible. The acute (observable) effects require minimal medical attention but may enhance stress-related casualties.

- Health Impacts Associated with Negligible Hazard Severity: Few, if any, persons expected to have noticeable (mild) health effects. The potential for individuals to have delayed (post-conflict) health concerns is considered minimal to none. Low-level exposures fall into this hazard severity category.

b. Defining Low-Level Exposures.

USACHPPM recommends that "low-level exposures" be doctrinally defined as exposures that represent a Negligible hazard severity as described above. (See Section 2.4 for more details.) Specifically, low-level chemical exposures do not produce health effects of significant physiological impact and, therefore, will not pose notable operational (mission) impact. This includes a range of exposures and points along a chemical's dose-response continuum—

- At the upper end of the range there is potential for some personnel to demonstrate mild, non-impairing, minimally noticeable acute reversible (temporary) effects.

- For certain chemicals, this range includes the possibility of delayed and/or non-clinical effects that may or may not be reversible.

- The levels near the lower bound of the low-level range are associated with no anticipated effects of any kind and should include consideration of those deployed personnel who may be genetically and/or physiologically predisposed to exhibit effects at lower levels than that of the average "healthy male military" population.

c. Specific Toxicity Values and Time Extrapolation.

It is concluded that, with appropriate extrapolation and adjustments to reflect data uncertainties and the potential for increased susceptibility (see Chapter 4), the DATSD-CBD interim-certified acute toxicity estimates can be used to define both the upper and lower bounds of the Negligible hazard severity range. Chemical-specific toxicity ranges derived from the DATSD-CBD interim-certified toxicity values and associated with all of the ORM hazard severity categories are described in Section 5 and summarized in Table 5-1. Detailed toxicity values are presented in Tables 5-2 through 5-4. Additional calculated values and presentations of toxicity ranges are also presented in Appendix F and G of this report. This level of chemical hazard characterization for these CWA is better and more detailed than what can be described for almost any other TIC. USACHPPM recommends this more detailed presentation of toxicity ranges for other potential key chemicals of concern and plans to pursue such an effort to improve military exposure guidelines presented in future versions of USACHPPM TG 230.

For many chemical defense applications, the acute CWA interim-vapor toxicity estimates, which are presented in units of milligram-minute per cubic meter (mg-min/m^3), would be more useful if they were converted to concentration units. The established criteria were limited for applications of 10 minutes or less. Inhalation vapor extrapolation to 24-hr exposure durations appears justified when an appropriate model is used (i.e., straight-line linear extrapolation is not always justified). Detailed information regarding time extrapolation is contained in Section 4.5.1. In addition, various conversions to provide duration-specific values for selected exposure durations (i.e., 10 min, 1 hr, 8 hr, and 24 hr) have already been calculated and listed in Appendix E.

d. Application of Operational Risk Management and Toxicity Estimates to Chemical Defense Measures.

The hazard severity ranges and associated toxicity criteria in Section 5 (Tables 5-1 through 5-4) provide the specific criteria necessary for various chemical defense applications. The recommendations for the specific hazard severity levels that apply to specific chemical defense applications are summarized in Table 5-6.

e. Chemical Defense Measures for Homeland Security.

Prior to the availability of the DATSD-CBD interim-certified toxicity values, USACHPPM had recommended the use of acute civilian vapor inhalation criteria established for emergency response scenarios (referred to as Acute Exposure Guideline Levels, or AEGLs) as criteria for certain military defense objectives. Comparison of values derived from the military DATSD-CBD set of vapor inhalation/ocular estimates to the AEGLs, shows that for the low-level exposure range, there is agreement once proper extrapolations have been conducted. For military applications, the DATSD-CBD interim-certified toxicity criteria (with extrapolations and adjustments as described in this report) should be used. For civilian applications, AEGLs, which have been Federally endorsed, should be used. Application of AEGLs has already been recommended by joint Army and Federal Emergency Management Agency policy for the Chemical Stockpile Emergency Preparedness Program.

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REPLY TO
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SECTION 1
INTRODUCTION

1.1 REFERENCES AND TERMS. References are listed in Appendix A. A Glossary is also provided at the end of this report listing acronyms and definitions of various terms used.

1.2 PURPOSE. To address a broad range of related issues associated with chemical risk assessment and operational risk decision making. While this report focuses on a specific group of chemical warfare agents (i.e., GA, GB, GD, GF, VX and HD) and exposure routes (i.e., inhalation, ocular, percutaneous), the concepts and recommendations extend to other chemicals (i.e., other warfare agents and toxic industrial chemicals (TICs)) as well as other exposure routes (i.e,. ingestion). Report guidance and recommendations address numerous questions that have been asked of the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) over the past several years by operational, medical, and research/acquisition audiences. The concepts and recommendations in this report are also being employed by USACHPPM to update previous guidance put forth in USACHPPM Technical Guide (TG) 230, *Chemical Exposure Guidelines for Deployed Military Personnel.*

The primary focus of this report is to provide implementing guidance and recommendations (with supporting rationale) pertaining to the use and interpretation of the December 2001 Deputy Assistant to the Secretary of Defense Chemical and Biological (Warfare Agent) Defense (DATSD-CBD)-endorsed acute interim-certified toxicity values for the chemical warfare agents (CWA) GA, GB, GD, GF, VX and HD. Specifically, this USACHPPM report explains the following:

(1) How toxicity information cited in the 2001 DATSD-CBD referenced report (referred to as the Institute for Defense Analysis or "IDA"R report) can be effectively incorporated into Operational Risk Management (ORM) terminology as required by Joint Staff guidance on Force Health Protection (FHP) and environmental surveillance (MCM, 2002a and 2002b).

(2) How the acute interim-toxicity estimates should be extrapolated and adjusted to address various questions (to include "what is low-level?") regarding different chemical defense measures (i.e., Modeling and Simulation (Planning and Prediction), Contamination Avoidance (Detection), Protection, Decontamination, and Medical Interventions).

Given the potential overlap of military and Homeland Security chemical defense measures, this report also includes a comparison of the military acute interim-certified toxicity estimates with other civilian toxicity-based guidelines.

The specific objectives of this USACHPPM report are—

- To translate established ORM definitions (DA, 1998) into terms relative to health impacts caused by chemical exposures, provide guidance on determining "acceptable risk" and define "low-level exposure levels." (See Section 2.)

- To identify the types of military applications (i.e., chemical defense measures) for which the Army incorporates acute CWA toxicity-based criteria and to establish the risk management objectives and conditions for each of these applications/measures to be addressed by the toxicity values. (See Section 3.)

- To evaluate the DATSD-CBD interim-certified acute CWA toxicity criteria in light of new data and guidelines, new concerns, and different methodologies for extrapolating the data, and to determine methods to derive a full range of toxicity values for ORM consideration. In particular, define specific toxicity ranges for the upper and lower bounds of the low-level and acceptable risk range. (See Section 4.)

- To recommend preferred and alternative toxicity-based values/extrapolation methods for each of the identified chemical defense measures, along with any critical decisions that need to be addressed by senior command levels before final criteria can be determined. (See Section 5.)

These analyses will help to address specific questions (such as those below) relating to applications of the CWA toxicity criteria. Answers to the following questions may vary for different applications, but most applications require a formal position on acceptable risk at a strategic level:

- Is our objective to establish basic conditions of mission success versus failure (the historical operational objective) or is it to identify and characterize all potential hazards (per recently established Joint Service and service-specific medical surveillance/FHP policies)?

- Is our objective to minimize death and severe casualties or is it broader than that, to include mitigating (to extent feasible) all health impacts?

- What level of confidence and/or degree of protection do we require for a given use of toxicity estimates?

- Does our objective require only consideration of average 70-kilogram (kg) male soldier susceptibility or do we need to factor in the greater susceptibilities resulting from genetic variability, gender, and/or other existing physiological conditions in the deployed force?

1.3 KEY ISSUES TO BE ADDRESSED

1.3.1 Operational Risk Management and Chemical Exposures

ORM is a process of assessing a hazard's severity and its probability to estimate a level of risk (i.e., Extremely High, High, Moderate, or Low). The ORM concept is embedded in almost every aspect of U.S. military operations, including the strategic, operational, and tactical levels. However, a historical exception to the use of the ORM process has been made with military chemical defense measures and doctrine, which have been largely established as a "go/no-go" single risk level system, in part due to lack of adequate human dose-response toxicity estimates.

The recent DATSD-CBD-endorsed interim toxicity estimates for GA, GB, GD, GF, VX and HD (as cited in the "IDA" Report), however, provide information that can now be used in military ORM applications. As currently documented, these toxicity criteria do not explicitly provide a single decisive go/no go "acceptable risk level," but rather demonstrate a range of effects levels. The availability of criteria that describe various levels of hazard severity, as they relate to mission impact, would provide a means to compare and/or balance chemical hazards with other risks to mission success in order to optimize the overall safety and success of a mission. In fact, recent Joint Staff guidance (MCM, 2002a and 2002) requires that exposures to chemicals (including CWA) during deployments should be identified and assessed and/or managed using established ORM doctrine.

Section 2 of this report provides an overview of the ORM process and translates existing doctrinal ORM definitions (as established in Army Field Manual (FM) 100-14, *Risk Management*, and FM 3-100.12, *Multi-Service Tactics, Techniques and Procedures for Risk Management*) into specific hazard severity definitions relating to health impacts caused by chemical exposures. It describes the variability of "acceptable risk" in military operations and examines and defines "low-level exposures" in terms of both ORM (i.e., mission success) as well as FHP.

***NOTE:** USACHPPM has previously provided operational chemical risk assessment guidance in TG 230 (USACHPPM, 2004). The ORM definitions in this USACHPPM report will be used in future updates of TG 230 to enhance and improve previously documented guidance and hazard severity definitions. Such enhancements have been recommended by the National Research Council (NRC) TG 230 review (NRC/Committee on Toxicology (COT), 2004).

1.3.2 Application of Chemical Warfare Agent Toxicity Values

Section 3 describes the specific scenarios requiring application of the CWA toxicity values for chemical defense measure decisions at strategic, operational, and tactical levels. Each scenario/chemical defense measure is described with respect to the ORM decisions and risk mitigation objectives/the degree of acceptable risk to be derived. In addition, parallel measures/scenarios that are used in Homeland Security initiatives are described.

1.3.3 Toxicity Estimates

In December 2001, the DATSD-CBD (DATSD-CBD, 2001) endorsed a document referred to as the "IDA report" (Grotte and Yang, 2001) that establishes interim-acute CWA toxicity values to be used for military applications. The IDA report (see Appendix B) documents the decisions made during a 1998 workshop of various military organizations (to include operational, research, analytical, and medical) as establishing a consistent set of toxicity estimates for analysts addressing chemical agent issues. During this workshop, members evaluated official existing military toxicity estimates presented in FM 3-9, *Potential Military Chemical/Biological Agents and Compounds,* against the proposed military toxicity estimates for the agents GA, GB, GD, GF, VX and HD established in a 1994 Army report referred to as the Reutter and Wade report (Reutter-Wade, 1994; this report is Secret except for Table 1, *Summary of Existing and Recommended Estimates (U);* see Appendix B). While the Reutter-Wade report provided the first thoroughly compiled assessment of all available data relating to the acute human toxicity of these agents, the toxicity estimates proposed in this report were in some cases significantly different (i.e., lower) than estimates historically used in military applications. There was a reported general consensus among workshop participants that many of the FM 3-9 values were not sufficiently conservative (low).

While there are controversial aspects of this issue, the IDA report reflects the consensus of a diverse military group employing best available data from that time. The report clearly documents its limitations, provides general guidelines for use, and describes future work to improve the data and resulting toxicity values. It, thereby, provides a significant point of reference for use in military applications.

The IDA interim-military toxicity estimates include two values for each endpoint: a baseline median population cumulative exposure and a probit slope. Median toxicity estimates are provided for lethality (lethal concentration (C) multiplied by time (t) for 50 percent population effect (LCt_{50}) and lethal dose 50 percent (LD_{50} values)), as well as for "threshold" and "severe" exposure concentrations ((ECt_{50} (threshold) and ECt_{50} (severe)). Toxicity values are provided for three different routes of exposure: inhalation/ocular vapor exposure, percutaneous absorption vapor, and liquid contact. Probit is a mathematical transformation used on percentile data to support extrapolations from a know data point.

The IDA report acknowledges various limitations of the cited information and identifies key issues that require further assessment. Primary concerns relate to the fact that the cited estimates: (1) focus on central median estimates with considerable uncertainty particularly when extrapolating to different percentiles; (2) are established for male military personnel and specifically not intended for mixed or civilian population use; and (3) are designated for very specific, short-term durations (minutes). The method for extrapolating over different exposure durations was not established. The IDA report also points out that probit–based extrapolation methods "may not be suitable for all cases" and that other methodologies should be explored.

***NOTE:** Since the 1998 IDA workshop, new research has begun to provide additional information that is useful in the application of these toxicity estimates. The increased focus on

the protection of military troops from chemical agents and other environmental hazards has also resulted in several new military policies on FHP and particular concern over "low-level" exposures to chemicals. This has spurred yet additional research and has also required a more in-depth review of these interim estimates, which do not specifically define which toxicity ranges reflect "low-level exposures". These interim estimates also do not specifically address how these toxicity estimates should be used relating to the recent (2001-2003) FHP policies and doctrine. Therefore, Section 4 summarizes the health effects associated with these agents and provides an evaluation of the most recent data along with various methods to extrapolate and or adjust the IDA-based toxicity values to represent the full range of ORM hazard severity/risk levels. Particular attention has been given to defining upper and lower bounds of the low-level range, including consideration of heterogeneous population susceptibilities, which can be used to address new FHP requirements. The resulting toxicity values (derived from officially endorsed IDA toxicity estimates) will be used to replace/update the military exposure guidelines (MEGs) for these agents in future versions of the USACHPPM TG 230 (USACHPPM, 2004).

1.3.4 Force Health Protection

Current Joint Chief of Staff (JCS) guidance, interim Department of the Army (DA) policy, and Joint (multi-service) and Army doctrine (MCM, 2002a; DA, HQDA 2001; Joint Publication (JP) 4.02, 2001; and DA, 2003c) indicate that FHP objectives (to include the assessment of chemical hazards) must now be incorporated into all operational decision making. Joint guidance (MCM, 2002b) indicates that CWA exposures or potential exposures should also be addressed according to established FHP policy and guidance. Most recently, the NRC has agreed that the military should assess and manage both CWA as well as other chemicals using the same operational risk management framework (NRC/COT, 2004).

These guidance documents, interim Army policy, and Army doctrine have come into affect since publication of the IDA report and require that chemical hazards, including those that cause immediate mission impact as well as those that pose only individual health impacts (even if minor or delayed), should be identified and considered. Specifically, the established JCS guidance and interim Army policy requires that chemical exposures of any significance to individual health be at least documented in the designated Department of Defense (DOD) environmental surveillance archive. To accomplish this, chemical defense measures should include appropriate tools and procedures to identify and assess these potential health hazards. As the interim-military toxicity estimates (i.e., IDA) provide median (50^{th} percentile) estimates for "70-kg male soldiers, not civilians or female military personnel," the use of these estimates as the basis for defining chemical defense measure specifications is not consistent with FHP requirements. These baseline median estimates require extrapolation/adjustment to reflect population thresholds (i.e., the level at which members of the exposed population will first begin to demonstrate initial effects). Such a "population threshold estimate" (PTE) should include consideration of a more demographically diverse military population which is likely to include susceptible individuals who would exhibit effects first, or at lower concentrations than the "average" personnel ("average" here meaning the demographic/fitness level and health status anticipated in a deployed population of 18 to 30-year-old Caucasian males with a good level of

fitness and few or no preexisting health conditions). The demographics of the military over the past decade exhibit an expanded ethnic diversity and increasing proportions of older personnel (30+ years) and females due to greater reliance on National Guard and Reserve forces (USACHPPM, 2004; USACHPPM 2003a, Appendix F, *The Role of Susceptibility in Establishing Exposure Standards for Deployed Troops*). At present, the deployed force is beginning to more closely resemble the general population in many respects. As described in Section 4 of this report, many of these individuals may be more susceptible to the effects of chemical agents than the "70-kg healthy male military" assumption reflected by the interim-military toxicity estimates.

***NOTE:** The degree with which chemical defense measures should address those who may be more susceptible is a key policy decision that has yet to be documented. This USACHPPM report identifies various applications that need to address FHP objectives and poses recommendations to DOD/Army policy makers and commanders for their resolution. Although such decisions must consider operational and technical feasibility, a formal position on acceptable risk at a strategic level must occur before a complete set of consistent toxicity estimates can be determined.

1.3.5 Consideration of Homeland Security Applications

Homeland Security joins civilian and military assets to meet a common challenge. The DOD is already considered the leader for chemical agent detection and monitoring equipment, personal protective equipment (PPE), tactics, and other areas of CWA expertise. Given that the majority of domestic civilian authorities have not independently evaluated CWA toxicity and developed CWA response guidelines, it is expected that Homeland Security authorities will look to the DOD for guidance and support in the event that a CWA release is anticipated or occurs. As a consequence, toxicity estimates underlying selection of civilian equipment may inherently be based on DOD policy and would be employed by other non-DOD entities. As the IDA report specifically states that the toxicity estimates are not for "civilian use," the military should acknowledge that there are other Federally endorsed CWA toxicity-based guidelines that are specifically designed for Homeland Security applications. This report evaluates the specific applications where toxicity estimates are incorporated into Homeland Security chemical defense measures and how those objectives compare with military objectives. Given the increased degree for protectiveness generally required for civilian applications, it is important to be aware of equipment limitations that derived from military technologies where some greater degree of risk was determined to be acceptable.

SECTION 2
OPERATIONAL RISK MANAGEMENT AND CHEMICAL EXPOSURES

2.1 RISK MANAGEMENT IN MILITARY DOCTRINE

"Risk" is a measure of the probability of harm or loss. "Risk management" is the process of identifying risks and weighing those risks and associated mitigating actions against a desired outcome and/or competing benefits. ORM can be used to refer to the application of risk management practice to military scenarios and decision making as defined by the specific risk management procedures documented in Army and Joint (multi-service) doctrine (e.g., FM 100-14 (DA, 1998); and FM 3-100.12 (DA, 2001)). This doctrine provides military commanders and decision makers with a standardized framework from which to identify, assess, control, and evaluate outcomes for a variety of military settings in a manner that enhances operational capabilities and mission accomplishment with minimal acceptable loss.

2.1.1 Key Principles

The basic principles underlying the ORM process are described in Table 2-1. These principles emphasize following the ORM framework at all stages of military operations - from planning to implementation and execution - by identifying hazards, assessing them on a standard risk characterization scale, and then ensuring that the appropriate information is made available to decision makers (i.e., risk managers) for accountable decision making, and closing the cycle with continued cyclic evaluation and modification.

Table 2-1. Principles of Operational Risk Management

Principle	*Description*
Accept No Unnecessary Risk	No one intentionally accepts unnecessary risks, but some risks may go unidentified. The risk management process requires first and foremost the identification of threats – and provides tools to assess, characterize, and balance associated risk with mission success. The most logical choices for accomplishing a mission are those that meet all mission requirements while exposing personnel and resources to the lowest acceptable risk.
Make Risk Decisions at the Appropriate Level	The risk management process must include those accountable for the mission: ensuring that risk decisions are made at the appropriate level will establish clear accountability. Each risk decision should be made at the level that has the authority and resources to eliminate or minimize the threat, implement controls to reduce the risk, or accept the risk.
Accept Risk When Benefits Outweigh the Cost	The process of weighing risks against opportunities and benefits helps to maximize mission success. Balancing costs and benefits is a subjective process and is a leader's decision.
Anticipate and Manage Risk by Planning	Integrating risk management into planning as early as possible provides leaders the greatest opportunity to make well-informed decisions and implement effective risk controls. During execution phases of operations, the risk management process must be applied to address previously unidentified risks while continuing to evaluate the effectiveness of existing risk control measures and modify them as required.

Properly incorporated into decision making, ORM enhances operational mission accomplishment by avoiding unnecessary risk to (thereby, preserving and protecting) personnel, combat weapon systems, and related support equipment. Proper use of ORM steps helps avoid common pitfalls of the risk assessment phase such as: overoptimism or alarmism ("It can't happen to us" vs. "The sky is falling"); personal prejudice or bias (deliberate or unconscious); indiscrimination (all data are given equal weight); or enumeration where overreliance on numbers may oversimplify real-life situations or, alternatively, may result in overconfidence in precision of risk estimates.

ORM, however, does not replace sound tactical decision making, nor should it inhibit a commander's or leader's flexibility, initiative, or accountability. In particular, ORM is not a means to remove risk altogether or support a zero-defect mindset. To the contrary, it should provide a logical basis for determining an acceptable risk for a given scenario.

2.1.2 Application of Operational Risk Management

In the ORM process, the level of risk associated with an identified potential hazard is determined through a two-step assessment process. The first step involves the deremination of hazard severity**,** which results in one of four qualitative severity levels (Catastrophic as most severe, to Negligible as least severe). The next step is to perform a probability assessment, which results in one of five qualitative probability levels (from frequent or very likely to unlikely). The probability assessment is usually supported by intelligence gathering, real-time observation, and forecasting techniques. The severity level and the probability level are then used in the standardized matrix represented by Table 2-2 to establish the risk estimate. The risk estimate is a qualitative descriptor of one of four levels (i.e., Extremely High, High, Moderate, and Low). Table 2-3 defines these levels of risk relating to operational impact and unit strength.

Table 2-2. Risk Assessment Matrix
(per FM 100-14)

		HAZARD PROBABILITY				
HAZARD SEVERITY		Frequent (A)	Likely (B)	Occasional (C)	Seldom (D)	Unlikely (E)
Catastrophic (I)	→	Extremely High	Extremely High	High	High	Moderate
Critical (II)	→	Extremely High	High	High	Moderate	Low
Marginal (III)	→	High	Moderate	Moderate	Low	Low
Negligible (IV)	→	Moderate	Low	Low	Low	Low
RISK ESTIMATE						

Table 2-3. Risk Level Definitions

Risk Level	Defined Consequence (FMs 3-100.12 and 100-14)	Unit Status (FM 101-5-1)*
Extremely High	Expected loss of ability to accomplish the mission.	Unit Requires Reconstitution. Unit below 50% strength.
High	Expected significant degradation of mission capabilities in terms of the required mission standard, inability to accomplish all parts of the mission, or inability to complete the mission to standard if hazards occur during the mission.	Combat Ineffective. Unit at 50 – 69% strength.
Moderate	Expected degraded mission capabilities in terms of the required mission standard will reduce mission capability if hazards occur during mission.	Mission Capable, with minor deficiencies. Unit at 70 - 84% strength.
Low	Expected losses have little or no impact on accomplishing the mission.	Mission Capable Unit at 85% strength or better.

* FM 101-5-1, *Operational Terms and Graphics.* The unit rates provided under unit status are to be determined by the commander. When interpreting risk-level definitions, one should not directly interpret the percentile of unit strength as equating to casualty or incidence estimates. More appropriately, hazard severity and associated risk levels should be associated with the anticipated array of direct health impacts (casualties) as well as indirect impacts (e.g. medical resources necessary to address those casualties as well as morale impacts to others).

2.2 DETERMINING ACCEPTABLE RISK

The concept of "acceptable risk" is difficult to define at a general level – particularly for the myriad of circumstances that affect military operations. At a minimum, risk may be acceptable if it does not lead to mission failure, but the type of mission can impact the level of acceptance. For instance, in high threat or "wartime" missions, a certain risk of casualties is anticipated and accepted. On the other hand, in peace-keeping or sustainment operations, even minor casualties may not be "acceptable."

For most scenarios, acceptable risks are those determined to be Moderate or Low (see Table 2-2) as they do not result in a combat ineffective unit. However, the first principle of ORM (see Table 2-1) calls for *accomplishing a mission … while exposing personnel and resources to the lowest acceptable risk.* Therefore, to the extent possible, Low risks are the objective whenever they can feasibly be met.

Determination of acceptable risk occurs generally at two levels of application: crisis action and deliberate. Crisis-action risk management is employed when considering risk while making decisions in a time-compressed situation with immediately available resources. This level of risk management is used during execution-phase operations and tactical environments as well as in planning and execution of responses to unplanned events. Deliberate risk management is the

application of the complete process when time is not critical. It primarily uses experience to identify threats and develop controls. This is typical of strategic planning.

At a strategic level of military decision making, deliberate risk management is required to define the bounds of acceptable risk on various issues that overlay a wide range of operational and tactical scenarios. These decisions must incorporate known impacts of operational and tactical risk (see Table 2-3) but should also consider non-constant factors such as mission requirements and public perception. Strategic decisions (such as the required detection level of a monitoring device) will impact the degree of risk knowledge and risk acceptance at the operational and tactical levels. In the case of a detector that does not detect certain hazards, those associated risks will go unknown, and inherently be "accepted."

2.3 APPLICATION OF OPERATIONAL RISK MANAGEMENT TO CHEMICAL HAZARDS

2.3.1 Force Health Protection and Operational Risk Management Requirements

There have been Joint (multi-service) and DA doctrine (JP 4-02, 2001; DA, 2001; and DA, 2003c) as well as JCS guidance (MCM, 2002a and 2002b) established that describes the necessary considerations and actions to address FHP goals. Specific guidance for addressing CWA exposures and potential exposures towards these FHP goals is also addressed in a separate Joint Staff memorandum (MCM, 2002b). This established doctrine and guidance (JP 4-02, 2001; DA, 2001; and DA, 2003c) requires the identification of all health risks and the use of ORM to determine whether it is reasonable and feasible to mitigate a health risk/threat, versus merely acknowledging (and documenting) its presence. The established doctrine and guidance also state that both immediate/acute health implications, as well as potential delayed or long-term health risks, should be considered in ORM decision making. A single ORM framework for assessing chemical risks (an approach recently commended by the NRC/COT (NRC/COT, 2004) is critical for field practicality.

It may be argued that consideration of health threats in operational decision making is a fairly significant departure from the established practice of only addressing medical threats and, therefore, does not fit the ORM paradigm. But in effect, the process has just been refined to require more specific consideration of the individual root causes of potential medical threats (USACHPPM, 2001). These terms are defined as follows (see FM 4-02.17, *Preventive Medicine Services*):

- Health threat refers to a hazard that poses risk to an individual soldier's health. The term can include hereditary conditions that manifest themselves in adulthood, individual exposure to an industrial chemical or toxin where others are not exposed, or conditions that can result in other injuries and traumas that affect an individual's health but may or may not affect the health of the unit (USACHPPM, 2001; USACHPPM, 2004).

- Medical threat refers to all *potential or continuing enemy actions and environmental situations that could adversely affect the combat effectiveness of friendly forces, to include wounds, injuries, or sickness incurred while engaged in a joint operation* (JP 4-02, 2001). In

Army and multi-service publications, the term is defined as a composite of all on-going potential enemy actions and environmental conditions and disease and non-battle injuries that may degrade a unit's combat effectiveness (as opposed to an individual's health).

As operational impacts drive ORM, clearly unit-based medical threats are more relevant than an individual health threat. In fact, operational risk definitions (Table 2-3) relate to impacts on a unit as opposed to an individual. Therefore, any health threat that doesn't significantly impact immediate unit operation (i.e., health threats that don't impact enough personnel or aren't sufficiently severe and immediate probably would not constitute a "medical threat") would be considered a "Low" risk. Military policy is to minimize overall risk to the operation. This necessarily means that when competing risks are present for a given time, location, or set of conditions, the greater risks are priorities. Therefore, in certain military situations, a "Low" risk may not be mitigated given that resources are prioritized to other higher risks. However, whenever feasible, all risks should be mitigated or minimized. Specifically, whenever practical, control measures for mitigating or minimizing low chemical hazards should be instituted. When they cannot be eliminated, current policy requires that chemical hazards (even low risk or negligible health risks) be specifically identified and documented.

In summary, FHP policies require, at a minimum, the identification and documentation of all chemical hazard health risks including even those that are not deemed substantial medical threats. Historically, only those health risks that clearly presented a unit/mission-impact were given operational attention. Current doctrine and guidance do not significantly change this focus but do require that some documentation and possible mitigation against any health risk be considered if individual troops are at risk. However, it is necessary to put such health risks in the context of ORM so that they can be given the degree of attention appropriate to the given scenario and mission.

2.3.2 Assessing Chemical Hazards with the Operational Risk Management Process

As described in paragraph 2.1.2., the ORM risk assessment process involves two steps: (1) determining the severity of a hazard; and (2) determining the probability of that hazard occurring. The severity of a chemical hazard is related to a dose, meaning that different doses will result in different types and severity of health effects (thus, the old saying "the dose makes the poison"). The dose, or cumulative exposure, necessary to cause a certain degree of health (and operational) impact will vary for different chemicals. For example, assume a teaspoon of chemical "X" is lethal to most people, while it would take a gallon of chemical "Y" to be lethal to most people. Each chemical can cause the same health impact (i.e., severity) but at different doses or cumulative exposures. In other words, the severity of one teaspoon of chemical "X" is equivalent to the severity of 1 gallon of chemical "Y."

When hazard probability is taken into consideration, one would consider the likelihood of a whole gallon of chemical "Y" being present versus a teaspoon of chemical "X." This probability assessment would evaluate intelligence information regarding the probability of each chemical being present or available at a location where an exposure could occur, and a determination as to

how likely that chemical would be released and disseminated, resulting in the specified dose or amount.

***Note:** This report focuses on the toxic effects and associated doses of the chemical agents, as opposed to dissemination methods and techniques. It provides recommendations on the severity-ranking component of the risk matrix. It does *not* address probability, as probability is a site- and scenario-specific determination.

2.3.3 Risk Levels Relative to Chemical Health Hazards and Casualties

In most scenarios, a chemical release will result in personnel exposures that will vary in duration and cumulative exposed concentration (dose). This will produce a range of health effects. The adverse health implications, particularly those that occur immediately during operations, will not only degrade mission success through limiting the number of capable persons (i.e., direct casualties), but depending on the severity, they can further drain mission resources through "buddy-assistance," transport, and medical treatment or care necessary for those injured or ill. In addition (and particularly with chemical-related incidents), mission focus and resources can be further diminished by psychological impacts associated with exposures. The degree of indirect impacts on mission success will depend on a variety of factors including the type and severity of effects, the type of mission/unit/tasks, and the environmental and logistical setting. As an example, some scenarios call for multiple persons to transport and/or assist in caring for one casualty, meaning that for every person affected, the unit loses more than one "warfighter." This may be considered a low or high estimate for other scenarios, but it demonstrates that the mission implications are broader than individual casualty estimation.

While it is impossible to exactly quantify the "indirect" mission impacts associated with chemical casualties, it is clear that the total mission impact will be greater than just that resulting directly from casualty loss. Indirect mission impact will vary widely depending on type of unit, training, resources, types of mitigating actions/treatment required, and operational tempo or "OPTEMPO." Even without precise estimates of indirect impacts, it is important to acknowledge their presence and operational significance. Specifically, it must be realized that casualty estimates are but a portion of the overall degradation of unit strength. When interpreting risk-level definitions represented in Table 2-3, one should not directly interpret the percentile of unit strength as equating to casualty or incidence estimates. More appropriately, hazard severity and associated risk levels should be associated with the anticipated array of direct health impacts (casualties) as well as indirect impacts (e.g., medical resources necessary to treat those casualties as well as personnel resources to provide transport and perform extra duties and morale impacts to others). Table 2-4 describes levels of hazard severity as an associated risk that may result from chemical exposures.

***NOTE:** While the determination of hazard severity levels for ORM is a military procedure not used in Homeland Security applications, the concept of addressing indirect impact as well as direct casualties is perhaps even a greater consideration in such civilian applications again to account for medical and non-medical resources required as well as the psychological impacts to the "unexposed."

Table 2-4. Hazard Severity Definitions and Associated Risk Levels for a Credible (Likely) Chemical Warfare Hazard

Hazard Severity	Health Impacts Associated with Hazard Severity Level	Hazard Probability*	Unit Status (FM 101-5-1)	Defined Consequence (FMs 3-100.12 and 100-14)	Risk Level
CATASTROPHIC	Increasing deaths and severe disabling/ incapacitating casualties requiring significant medical attention (e.g., Echelon IV) and/or additional personnel support for survival.	Assume "Likely"	Unit Requires Reconstitution. Unit below 50% strength.	Expected loss of ability to accomplish the mission.	**Extremely High**
CRITICAL	Few, if any, deaths but significant numbers of disabling/incapacitating casualties, many requiring medical treatment or support (e.g., minimum Echelon III, possibly Echelon IV); others are likely to have noticeable but not disabling health effects.	Assume "Likely"	Combat Ineffective. Unit at 50 – 69% strength.	Expected significant degradation of mission capabilities in terms of the required mission standard, inability to accomplish all parts of the mission, or inability to complete the mission to standard if hazards occur during the mission.	**High**
MARGINAL	Many persons may have noticeable but not disabling health effects and/or the potential for individuals to have reversible, delayed (post-mission or deployment) health effects is considered very possible. The acute (observable) effects require minimal medical attention but may enhance stress-related casualties.	Assume "Likely"	Mission Capable, with minor deficiencies. Unit at 70 - 84% strength.	Expected degraded mission capabilities in terms of the required mission standard will reduce mission capability if hazards occur during mission.	**Moderate**
NEGLIGIBLE	Few, if any, persons expected to have noticeable health effects. The potential for individuals to have delayed (post-conflict) health concerns is considered minimal to none. Low-level exposures fall into this hazard severity category.	Assume "Likely"	Mission Capable Unit at 85% strength or better.	Expected losses have little or no impact on accomplishing the mission.	**Low**

*As stated in text, the probability of the hazard occurring is a site- and scenario-specific determination; for purposes of this report and table, the "likely" probability is assumed to demonstrate the relationship of hazard severity to risk in a credible-event scenario. See Appendix C, Table C-3, for definitions of the probability categories.

2.4 LOW-LEVEL CHEMICAL EXPOSURES DEFINED IN OPERATIONAL RISK MANAGEMENT TERMS

"Low-level" exposures have become a high priority to the military and its research community especially due to the experiences during and after Operation Desert Storm and resulting evaluations of potential causes of Gulf War Illness. This has resulted in increased emphasis on FHP concerns related to the potential health effects resulting from exposures to CWAs as well as other chemicals. The threat of exposures to low-level CWAs has been described (DOD, 2003) as—

- Deployment downwind or on the periphery of an actual CWA attack and/or CWA release.

- Entry into an area after a CWA attack.

- Exposure to agent from partially decontaminated materiel, supplies, or surfaces.

Though the term "low-level chemical exposures" has been frequently used over the past few years in reference to various issues, such as exposures associated with potential delayed health effects and detection level objectives, no Army (or military) doctrinal definition has been formally established. The DOD has proposed general interpretations in strategic research documents (DOD, 1999; DOD, 2003). The first of these documents described such exposures as being represented by cumulative doses (as a factor of concentration and time) "below which no significant adverse health effects (immediate or delayed) are presumed to occur according to best available science." The more recent document (*DOD Low-Level Chemical Warfare Agents (CWAs) Exposure Research Plan*, Final Draft, DOD, 2003) refines the previous definition as—

> *Exposure concentrations (for specified durations and frequencies) likely to be experienced by DoD personnel below which there are no immediate observable adverse health effects or operationally relevant performance decrements projected for healthy DoD personnel using accepted toxicological tests and standard medical practices.*

The final draft DOD Low-Level Research Plan (DOD, 2003) further defines the terms "operationally relevant performance decrements" as—

> *An impairment of performance during a military operation resulting from either temporary or short-term low-level exposures to a CWA experienced during that military operation.*

This research plan goes on to describe other effects that are different points along the dose-response continuum including potential delayed adverse health effects (i.e., effects that occur after the mission has ended, and possibly not until months to years after an exposure incident) and clinically insignificant effects (i.e., effects that may/may not be outwardly noticeable but do

not impact personnel functionality and are not shown to have a specific adverse health impact (immediate or delayed)). What is not clear in this research plan (DOD, 2003) is whether (assuming that delayed effects and clinically insignificant effects occur at exposure levels below those which cause no immediate observable adverse health effects or operationally relevant performance decrements projected for healthy DOD personnel) these would necessarily still be considered low-level exposures.

Despite these attempts at defining "low-level," there is no current uniform military definition, which has lead to disparate decision making and research objectives. A standard definition of low-level exposures is needed to focus strategic decisions and research, to standardize chemical defense measure objectives, and to communicate risk at the operational and tactical levels. USACHPPM proposes using the existing ORM framework to derive a definition of low-level exposure. The following definition of low-level exposures is recommended for uniform military use and incorporation into doctrine:

"Low-level exposures" include chemical exposures that result in impacts that are of **Negligible hazard severity**. Specifically, low-level chemical exposures do not produce health effects of significant physiological impact and, therefore, will not pose notable operational (mission) impact. This includes a range of exposures and points along a chemical's dose-response continuum:

- At the upper end of the range there is potential for some personnel to demonstrate mild, non-impairing, minimally noticeable acute reversible (temporary) effects.
- For certain chemicals, this range includes the possibility of delayed and/or non-clinical effects that may or may not be reversible.
- The levels near the lower bound of the low-level range are associated with no anticipated effects of any kind and should include consideration of those deployed personnel who may be genetically and/or physiologically pre-disposed to exhibit effects at lower levels than that of the average "healthy male military" population.

As previously described in paragraph 2.3.3, the levels of exposures that may be considered an "acceptable risk" may include those of Marginal severity (Moderate Risk). However, as previously noted, the primary ORM principle is to accomplish a mission while exposing personnel and resources to the lowest level of risk feasible. This practice, together with the recent FHP requirements, necessarily results in increased focus on Negligible hazards.

Table 2-4 describes Negligible chemical hazards as those chemical exposures (defined by concentration over time) that result in *Few if any persons expected to have noticeable health effects,* and for which the *potential for individuals to have delayed (post-conflict) health*

concerns is considered minimal to none. It is necessary to emphasize that chemical exposures of Negligible hazard severity (as well as any category of greater hazard severity) are represented by a *range* of exposure levels (as opposed to a single specific dose or concentration) and range of effects, which can be described by an upper and lower bound. This concept is further depicted in Figure 2-1.

Figure 2-1. Representation of Low-Level Exposures Relative to Operational Risk Management Severity Levels

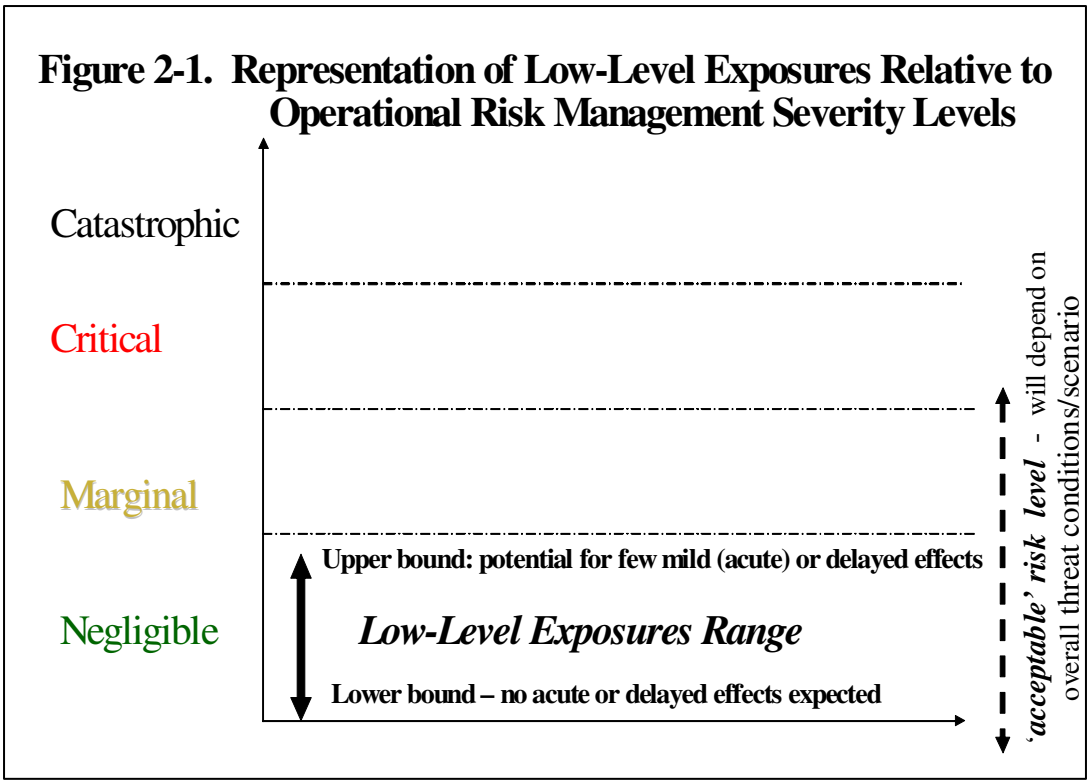
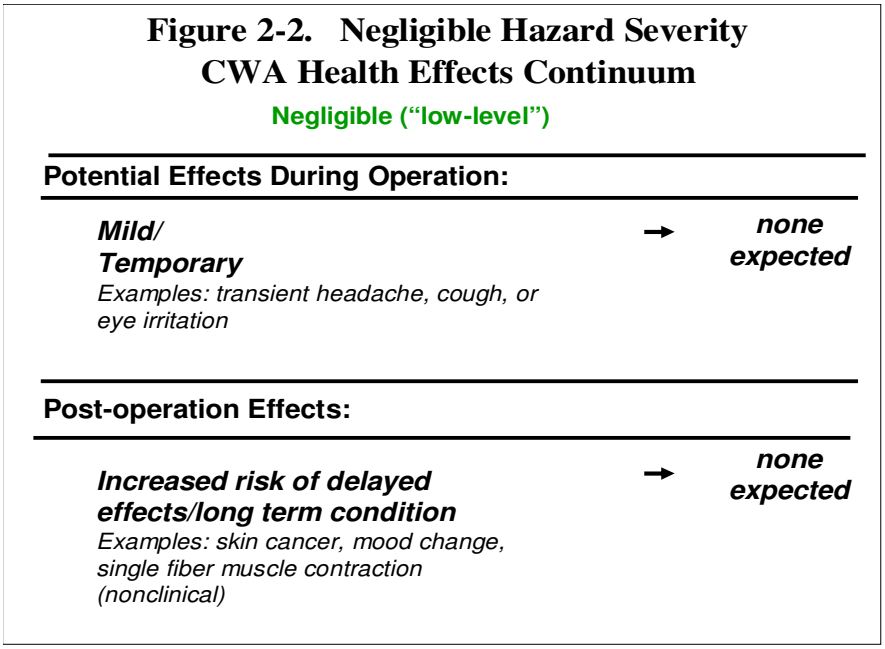


Figure 2-2 provides a more detailed description of the types of effects within the Negligible hazard severity range that could result from low-level exposures to nerve or mustard CWA.

Figure 2-2. Negligible Hazard Severity CWA Health Effects Continuum



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SECTION 3
CHEMICAL WARFARE DEFENSE MEASURES REQUIRING TOXICITY INFORMATION

This section summarizes the elements of chemical warfare defense and suggests key objectives for each element in terms of hazard severity and low-level exposure definitions presented in Section 2.4. To a large extent, these measures can have similar applications in Homeland Security scenarios, though some unique considerations apply. As various military organizations and resources (e.g., personnel, models, detection, and/or protection equipment) may be called upon for civil support, the last portion of this section addresses some of the unique considerations that apply to these Homeland Security scenarios.

3.1 CHEMICAL WARFARE DEFENSE MEASURES AND OBJECTIVES

Chemical warfare defense measures are designed to improve the capability of personnel to survive and sustain operations in chemical warfare environments through avoidance and/or mitigation of chemical exposures. Elements of chemical defense include Modeling and Simulation (Prediction), Contamination Avoidance, Protection, Decontamination, and Medical Interventions. Each of these areas requires consideration of agent toxicity and associated effects levels. However, as described in Section 2 of this report, existing doctrine and guidance have not specifically defined chemical exposures in terms of ORM risk levels or hazard severity definitions. Instead, chemical defense applications have directly incorporated specific numerical population effect estimates for selected toxicity endpoints (i.e., fatalities, incapacitating effects, and mild effects) without defining the level of risk or hazard severity reflected by such estimates. This approach can lead to inappropriate conclusions (e.g., the perception that any agent detected will result in death if not protected against, or alternatively, the assumption that the point of mission failure occurs at or above a 50 percent fatality rate, as opposed to well below that level where many incapacitating (though not lethal) effects will occur). In addition, existing doctrinal and guidance language have yet to specifically address the issue of “low-level” exposures.

Therefore, in this section, key objectives for each element of chemical defense measures are proposed in terms of the hazard severity and low-level exposure definitions presented in Section 2.4. An agreement of these objectives and the risk levels to be addressed is a critical step towards ensuring appropriate use of chemical toxicity values.

3.2 MODELING AND SIMULATION/PREDICTION AND PLANNING

Computer modeling has become an essential component of military operations, primarily as a prediction and planning tool. There are two types of modeling and simulation/prediction and planning currently in use: (1) vulnerability or threat assessment, which includes predictive contamination impacts and casualty estimation; and (2) FHP occupational and environmental health (OEH) hazard surveillance.

3.2.1 Vulnerability Assessment, Hazard Prediction, and Casualty Estimation

These applications allow commanders to determine the potential effects of agent contamination on current and future operations. In the nuclear, biological, or chemical (NBC) arena, vulnerability or threat assessments include modeling of potential scenarios involving chemical agent attacks and releases. Modeled plumes are overlaid with personnel locations to estimate potential casualties and related operational risks. This information can be used to plan for major resources and to choose alternative courses of action. Casualty estimation is a critical component to these applications as it provides information directly associated with unit strength operational impact and can be used to determine approximate medical resource needs or indirect personnel impacts. In the event that an event occurs, vulnerability modeling may be performed again or assessed against real-world data (detector results). Specific parameters to consider in the selection of toxicity criteria to be used in such modeling and prediction are described in Table 3-1.

Table 3-1. Toxicity Criteria Selection Factors for Modeling and Simulation/Prediction and Planning Vulnerability Assessment, Hazard Prediction, and Casualty Estimation

Key Objective(s):	- Identify/prioritize areas of concern; - Predict extent of problem.
Associated hazard severity levels of concern:	- All, but primary focus on Catastrophic, Critical, (and Marginal). (See Table 5-1 for detailed toxicity criteria.)
Need to address individual health threats and/or low-level exposures.	- No – focus is on medical (operational) threats.
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Both (casualty estimates often desired).
Confidence required/Uncertainty acceptable?	- Accept data gaps/uncertainty as is.

3.2.2 Force Health Protection-Occupational Environmental Health Surveillance

Current JCS FHP guidance (MCM, 2002b) requires documentation of potential troop (individual) exposures to chemical agents. This guidance also relies on modeling of plumes, which are then overlaid with personnel locations. Unlike vulnerability assessments, however, these FHP modeling efforts consider impacts to individual health and specifically identify the lower bounds of the Negligible hazards for required OEH exposure documentation purposes. Though sometimes used as a form of preventive planning/avoidance, modeling and simulation for FHP and surveillance aspects of CWAs will likely be a post-event modeling activity. Modeling results may be validated or embellished with real-world data (detector results). Specific parameters to consider in the selection of toxicity criteria to be used in FHP modeling and prediction are described in Table 3-2. Since in most instances actual measurements are not routinely available, FHP modeling is normally employed. It is noted that when conducting FHP modeling, particularly with single or short-term releases (such as would be expected with CWA incidents), it is critical that appropriate acute toxicity criteria (as opposed to long-term, chronic safety standards) are used to assess and/or determine exposures of concern.

Table 3-2. Toxicity Criteria Selection Factors for Modeling and Simulation/Prediction and Planning FHP-OEH Surveillance	
Key Objective(s):	- Identify areas of potential exposure; - Prioritize/rank exposure of concern.
Associated hazard severity levels of concern:	- All (Catastrophic-Negligible). (See Table 5-1 for detailed toxicity criteria.)
Need to address individual health threats and/or low-level exposures.	- Yes – need to document those "exposed and potentially exposed" (MCM, 2002b).
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Risk levels (and associated health impacts of concern).
Confidence required/Uncertainty acceptable?	- Incorporate/account for uncertainties (err toward overestimating exposures).

***Note:** During the various post-event modeling of the potential exposures resulting from the Gulf War Khamisiyah Pit demolition incidents of 1991 (DOD, *U.S. Demolition Operations at Khamisiyah, Final Report*, April 16, 2002), "exposures" were determined through plume models using criteria designed to be protective of the general population for 24-hour per day lifetime (70-year) exposures. Toxicity criteria described and recommended in this report would have been more appropriate criteria for assessing that event, had such criteria been available.

3.3 CONTAMINATION AVOIDANCE (DETECTION AND IDENTIFICATION)

Contamination avoidance is a broad area that includes all of the actions taken to minimize the impact of NBC contamination on operations. Specific measures that require toxicity criteria applications include detection and identification, prediction, and sampling.

Chemical agent detection and identification activities provide commanders with the information needed to determine protective postures and to tailor protective actions to the specific agent threats. Early detection provides more time to implement protective measures. Accurate identification of agents enables selection of the most effective protective actions, including medical treatment, and limits mission degradation that results from taking unnecessary actions. Chemical agent detection and identification includes the use of point and standoff detection methods, risk assessment, and all available medical and non-medical intelligence assets.

3.3.1 Detection for Warning and Protection

3.3.1.1 Point Detection

Point detection devices/equipment (such as M256, Improved Chemical Agent Monitor, and Drager tubes (see Appendix D)) provides local and individual health threat information in real-time mitigation of the health risk. Ideally, such equipment should identify whether any health threat is present and should also be able to either indicate a range of agent concentrations or demonstrate the level of hazard the agent poses. This may be accomplished through a numerical display of the agent levels or through a tiered alarm system. This information can, in turn, be used to determine protective posture, decontamination, and other actions. If equipment provides a single "go-no go" alarm, limited flexibility is offered to the Commander to consider site and mission-specific needs and competing risks. Clearly, achieving low-detection levels must be balanced with other critical specifications such as timely (real-time in minutes), accurate readings with limited false positives. Achieving detection limits that represent a true "no-risk" level are not likely feasible. Instead, levels that provide reasonable warning against significant individual health risk should be considered reasonable. Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding point detection (alarm) goals are described in Table 3-3.

Table 3-3. Toxicity Criteria Selection Factors for Point (Warning) Detection

Key Objective(s):	- Identify health threat (to prevent). - Prioritize/rank degree of severity.
Associated hazard severity levels of concern:	- Focus is to achieve detection of Negligible chemical hazards (which will also address more significant hazard levels). (See Table 5-1 for detailed toxicity criteria.)
Address individual health threats/low-level exposures.	- Yes (at a minimum the upper bound of the low-level (Negligible) range is desired; lower bound is ideal).
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified detection thresholds, objectives necessary (from Negligible severity range).
Confidence required/Uncertainty acceptable?	- Ideally - incorporate/account for uncertainties (err by overestimating exposures).

3.3.1.2 Stand-Off Detection

Standoff detection devices provide additional time to implement protective measures or avoidance before exposure to agent occurs. Detection must occur at sufficient distances upwind of personnel to provide a reasonable amount of time for detection, processing, and information transmission. Toxicity criteria are important for defining the "edge of an agent plume," but overall, the associated technology is not overtly sensitive to low concentrations. Because this technology provides an added element of time, the standoff systems do not necessarily need to be as protective as point detectors. Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding standoff detection goals are described in Table 3-4.

Table 3-4. Toxicity Criteria Selection Factors for Stand-Off Warning Detection	
Key Objective(s):	- Warn against medical (unit) threat. - Prioritize/rank degree of severity.
Associated hazard severity levels of concern:	- All, but focus is to achieve detection of Marginal or even Negligible. (See Table 5-1 for detailed toxicity criteria.)
Address individual health threats/low-level exposures.	- This level of refinement not necessary for standoff detection.
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified detection thresholds, objectives necessary (from Marginal or Negligible severity range).
Confidence required/Uncertainty acceptable?	- Accept data gaps uncertainty as is.

3.3.2 Detection for Verification

Detection for verification provides critical information to support decisions concerning the need for tailored responses to chemical warfare events. Unfortunately, absolute confirmatory analyses require samples to be obtained and transported to a rear-area laboratory. These analyses may take days or weeks. Therefore, a variety of more specific or accurate field (point) systems/equipment in existence or under development provides a mechanism for "field verification" as a more time-efficient verification of point or standoff alarm systems. Field verification equipment should be able to determine accuracy of point detection systems described above. Ideally, these systems would be able to specify agent type and quantities present. Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding field verification/confirmation goals are described in Table 3-5.

Table 3-5. Toxicity Criteria Selection Factors for Field Verification/Confirmation	
Key Objective(s):	- Verify health threat. - Prioritize/rank degree of severity.
Associated hazard severity levels of concern:	- All but primary focus is to specifically identify type of agent at even negligible levels of severity. (See Table 5-1 for detailed toxicity criteria.)
Address individual health threats/low-level exposures.	-Yes (at a minimum the upper bound of the low-level (Negligible) range; ideally the lower bound).
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified detection thresholds, objectives necessary (from Negligible severity range).
Confidence required/Uncertainty acceptable?	- Ideally - incorporate/account for uncertainties (err toward overestimating exposures).

3.3.3 Detection for Surface Contamination

Detection for surface contamination is the ability to detect deposited contamination on surfaces in an area of identified concern. The results are used to determine the need for area avoidance, immediate or operational decontamination, and appropriate protective equipment. They may support the need to use alternate routes to avoid contaminated terrain if personnel cannot wait the short time period required for agent absorption. Results may also be used to adjust protective measures for people handling contaminated material. Particularly in time-critical scenarios

where off-gassing is limited (such as with more persistent agents VX and sulfur mustard (HD) and/or in colder climates and weather) field surface sampling/wipe detection kits will be critical decision-making tools (though use of point source detectors for toxic gases/vapors is still generally advised). Ideally, quantified or tiered levels of severity ranges could be interpreted from future equipment. At a minimum, gross contamination posing potential mission impacts should be identified (levels based on percutaneous liquid toxicity criteria). Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding detection of surface contamination are described in Table 3-6.

Table 3-6. Toxicity Criteria Selection Factors for Detection of Surface Contamination

Key Objective(s):	- Identify health threat (to prevent). - Verify decontamination.
Associated hazard severity levels of concern:	- All - but depending on objective, primary focus may be to identify marginal or greater hazards. For decon, verification detection of Negligible levels of severity desired. (See Table 5-1 for detailed toxicity criteria (for percutaneous liquid).)
Address individual health threats/low-level exposures.	- Yes for decon verification (at a minimum, the upper bound of the low-level (Negligible) range is desired; lower bound is ideal).
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified detection thresholds, objectives necessary (from Negligible severity range for decon verification).
Confidence required/Uncertainty acceptable?	- Ideally - incorporate/account for uncertainties (err toward overestimating exposures).

3.3.4 Detection for De-warning/De-Mission-Oriented Protective Posture

Detection for de-warning means detecting to identify when contamination has reduced to levels that permit removal of the protective mask or to de-mission-oriented protective posture (MOPP). Since CWAs can remain or persist much longer on some surfaces and off-gas at differing rates, de-warning should be based on a combination of devices/equipment for sampling and testing surfaces as well as air concentrations.

As previously described, real-time local and individual exposure information that can be used to establish degree of risk (as opposed to “go- or no–go” criteria) provides the necessary flexibility for optimum ORM. MOPP options can be used to extend operations, but they are not the solution for every situation. Most commanders know they cannot expect the same work rates in MOPP 4 as achieved in MOPP 0. Depending on the task and climate, the consequences to personnel from wearing MOPP may range from insignificant (i.e., cool or mild conditions) to catastrophic (i.e., hot and dry conditions). When contamination is present, the commander must be prepared to choose between mission accomplishment chemical defense and agent effects on personnel. Therefore, MOPP-reduction decisions are difficult to make because of the many considerations (e.g., toxicity levels, temperature, activity levels, and competing risks) that affect

the final decision. Therefore, de-warning systems (as a form of point detection/verification) need to provide a range of toxic hazard severity so that the staff will be prepared with the information the commander needs to select an appropriate course of action. Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding de-MOPP are described in Table 3-7.

Table 3-7. Toxicity Criteria Selection Factors for De-Warning/De-MOPP	
Key Objective(s):	- Monitor/identify health threat severity.
Associated hazard severity levels of concern:	- Focus is on identifying Marginal and Negligible hazard conditions.
Address individual health threats/low-level exposures.	- Yes (at a minimum, the upper bound of the low-level (Negligible) range is desired; lower bound is ideal). (See Table 5-1 for detailed toxicity criteria.)
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified detection/monitoring criteria necessary (from Marginal to Negligible severity range (ideally - upper and lower bounds of Negligible range).
Confidence required/Uncertainty acceptable?	- Ideally - incorporate/account for uncertainties (err toward overestimating exposures).

3.4 PROTECTION

Protection provides the force with survival and sustainment measures to operate in an NBC environment when contamination cannot be avoided. Protection is provided by individual protective equipment (IPE) and collective protection. The design goals for both individual as well as specific collective protection systems and equipment should be to minimize the chemical threat while providing maximum operational readiness in even the worst, high-level agent environments.

3.4.1 Individual Protection

Individual protection includes IPE such as respiratory protective equipment (e.g., masks/ respirators/cartridges) and chemical protective suits or ensembles. Masks/goggles and associated cartridges and breathing apparatus must, at a minimum, prevent vapor inhalation and ocular effects at catastrophic high (i.e., fatal) levels and should provide an "internal environment" of negligible health severity. Suit ensembles need to protect against similar levels of risk relating to percutaneous vapor absorption (especially to susceptible body regions such as the head, neck, groin, and armpits). Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding individual protection goals are described in Table 3-8.

***NOTE:** In Homeland Security scenarios, military and civilian responders may be required to where commercial IPE (referred to as personal protective equipment or PPE. It is important to verify that commercial PPE is adequately protective for CWA. For civilian applications, there may be the need for more protective PPE objectives (e.g., see ORNL, 2003).

Table 3-8. Toxicity Criteria Selection Factors for Individual Protection	
Key Objective(s):	- Prevent exposure resulting in effects.
Associated hazard severity levels of concern:	- All – design criteria should include testing against Catastrophic levels of exposure but goal should be to provide an 'internal environment' of Negligible severity.
Address individual health threats/low-level exposures.	- Yes (at a minimum, the upper bound of the low-level (Negligible) range is desired; lower bound is ideal). (See Table 5-1 for detailed toxicity criteria.)
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified "break-through" testing criteria needed to ascertain goal for maximum exposures acceptable with mask and ensembles.
Confidence required/Uncertainty acceptable?	- Account for uncertainties to extent feasible (err toward overestimating exposures).

3.4.2 Collective Protection

Collective protection may be incorporated into hardened or unhardened facilities or added to field expedient shelters to provide areas that are safe from toxic levels of agent without use of IPE. While it is unlikely that such areas can be guaranteed as "agent free," at a minimum they should prevent exposures that could pose even marginally severe health effects. Ideally, they will prevent exposures that pose even negligible health effects. Certain types of shelters may require greater confidence in the protective levels desired. For instance, collective protection units used for medical treatment must ensure an environment where medical personnel can conduct their activities without IPE and without suffering mild health effects that could detract from their capabilities. Collective protective systems should be able to maintain protective levels for several hours (up to 48 hours). Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding collective protection goals are described in Table 3-9.

Table 3-9. Toxicity Criteria Selection Factors for Collective Protection	
Key Objective(s):	- Prevent/minimize exposure.
Associated hazard severity levels of concern:	- All – design criteria should include testing against Catastrophic levels of (external) exposure but goal should be to provide an "internal environment" of Negligible severity.
Address individual health threats/low-level exposures.	- Yes (at a minimum, the upper bound of the low-level (Negligible) range is desired; lower bound is ideal. (See Table 5-1 for detailed toxicity criteria.)
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified "break-through" testing criteria needed to ascertain goal for maximum internal exposure levels.
Confidence required/Uncertainty acceptable?	- Account for uncertainties to extent feasible (err toward overestimating exposures).

3.5 CONTAMINATION CONTROL (DECONTAMINATION)

Contamination control is a combination of standard exposure prevention measures and traditional decontamination measures. Decontamination operations include individual, team, and unit actions. These actions reduce, remove, weather, or neutralize (i.e., render harmless) the primary hazards resulting from NBC contamination in order to prevent or minimize mission-performance degradation, casualties, or loss of resources. There are various degrees of decontamination ranging from initial life-saving procedures to more detailed patient decontamination to more thorough measures required to bring an area or item back to normal/unrestricted use. In military settings, decontamination efforts should be balanced with other mission requirements and competing risks and at times more thorough decontamination may not be a priority.

***NOTE:** In Homeland Security situations, while there still may be an initial or gross decontamination phase, the focus will quickly shift to ensuring thorough and complete decontamination has been achieved.

3.5.1 Levels of Decontamination

The Joint Services conduct decontamination operations at three levels: Immediate, Operational, and Thorough. Table 3-10 outlines the decontamination levels, purpose for each level, who does the task, what is decontaminated, and when the operation will be conducted, and provides guidance for selection of toxicity criteria (based on hazard severity levels) to apply in contamination control.

3.5.2 Methods of Decontamination

Under some conditions, decontamination activities can help sustain or enhance operations by allowing MOPP reductions, preventing contamination spread, and reducing casualties and material contamination. However, there is no single procedure, machine, kit, or technique presently capable of fulfilling all decontamination requirements. Present decontamination methods require that commanders evaluate mission needs and the threat situation, identify a desired result from a successful decontamination operation, determine what resources and methods are available, and decide on a course of action that can realistically reach the desired outcome. With the exception of personnel and medical patient decontamination, natural decontamination (e.g., use of decay, weathering and time) is the most cost-effective and easiest of the decontamination methods for facilities, large equipment, and terrain. Under most wartime conditions, commanders should not attempt thorough decontamination operations for material, vehicles, munitions, equipment, aircraft, or terrain unless the anticipated result significantly reduces a mission-degrading hazard or allows a mission-critical MOPP reduction.

Table 3-10. Levels of Decontamination and Recommended Certification

Level	Purpose	Who	What	When	Certification Method	Objective(s), Risk, and Severity
Immediate	Minimize casualties, save lives, and help limit contamination exposure and spread.	Individuals	Skin, personal clothing and equipment, frequently touched surfaces.	As soon as contamination is suspected or detected.	None (procedure based) or surface detection.	Obj: minimize casualties/save lives. Severity levels of concern: Catastrophic, Critical (See Table 5-1.) Detection types- none -gross (surface detection)
Operational	Limit contamination exposure and spread, helps to sustain operations by providing temporary and, in some cases, long-term relief MOPP.	Individuals, crews, teams, units.	Parts of essential operational equipment, work areas, vehicles, and material.	For MOPP level reduction; when operations require and resources permit.	Surface and point detection.	Obj: minimize casualties/save lives. Severity levels of concern: Catastrophic, Critical, Marginal (See Table 5-1 for detailed toxicity criteria.) Detection types - surface detection (gross) - point (air) detection
Thorough	Reduce or eliminate the need for wearing MOPP.	Units or wings, with or without external support.	Personnel, equipment, material, vehicles, aircraft, work areas, terrain.	When required for (total) MOPP removal; when operations, manning, and resources permit; required for total reconstitution and return to unrestricted use.	Field verification *Negligible* hazard levels; return to unrestricted use may require confirmatory verification official laboratory analyses.	FIELD USE: Obj: eliminate need for IPE, reconstitute Severity levels of concern: Marginal, Negligible (upper/lower bounds)* (See Table 5-1.) Detection types - surface detection (gross) - point (air) detection UNRESTRICTED USE (to CONUS): Obj: eliminate hazard Severity: Negligible (lower bound) (See Table 5-1.) Quantitative: - surface verification - point (air) verification

*Thoroughness of decontamination and degree of confidence will depend on type of scenario, equipment, and tasks needing to be performed.

3.6 MEDICAL INTERVENTIONS/COUNTERMEASURES

Medical interventions and countermeasures include pretreatment and "theraputic" (or post-exposure) treatment. An example of pre-treatment includes pyridostigmine bromide (PB) taken when a chemical warfare attack is anticipated to enhance the effectiveness of available therapeutic antidotes atropine and 2-protopam (2-PAM) chloride.

As with protective measures, a key objective focus for pretreatment and post-treatment intervention is the ability to mitigate effects of worst case, high-level exposures that would otherwise result in lethal or severely injurious effects to personnel.

Criteria used to assess "adequacy" of pretreatment and therapeutic medical intervention for CWA exposures are currently based on The Technical Cooperation Program (TTCP) Minutes of the 15-16 October 1981, Subgroup E Technical Panel Meeting (TTCP, 1981) stating that "the pretreatment when supplemented with therapy should enable subjects to survive poisoning by at least 5 x LD_{50} (50 percent lethal dose) dose of agent." The U.S. has followed this decision with the additional requirement that pretreatment therapy alone should be able to protect against 2 x LD_{50} exposure.

As serious injury and death can still occur at substantially less than an LD_{50}, more flexible criteria for interventions being considered in research and development/technology development may be useful to increase options and tools. But clearly, such interventions must be able to provide substantial benefit against extreme and high risks in conjunction with minimal adverse side effects. Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding medical intervention/countermeasure goals are described in Table 3-11.

Table 3-11. Toxicity Criteria Selection Factors for Medical Intervention/ Countermeasures

Key Objective(s):	- Prevent fatalities/minimize severity. - Mitigate impacts of high-level exposures (lethal and incapacitating).
Associated hazard severity levels of concern:	- Testing criteria should include lethal (Catastrophic) levels; goal is to reduce/eliminate health effects. (See Table 5-1 for detailed toxicity criteria.)
Address individual health threats/low-level exposures.	- Minimize adverse side effects.
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified testing criteria needed to ascertain maximum effectiveness.
Confidence required/Uncertainty acceptable?	- Ideally, account for uncertainties.

3.7. HOMELAND SECURITY/CIVIL SUPPORT APPLICATIONS

The military plays a supportive role in Homeland Security/Civil Support planning, emergency response, and post-event consequence management activities. Such activities will likely include similar types of chemical defense measures and involve the use of some equipment that is the same as or similar to that used by the military in deployments. However, the procedures and decision making for Homeland Security, which will be determined by non-military Federal or state agencies, will not be based on the previously described ORM framework. Certain decisions or actions determined for the civilian scenarios require more confidence in the extent and level of protection offered. Also of note is that the established military interim-certified toxicity estimates (DATSD-CBD, 2001), which are the primary subject of this report, are specifically applied to "healthy male military personnel" and are *not* to be used for civilians. Instead, there are Federally endorsed acute-vapor, toxicity-based values for the nerve agents and HD that are specifically developed for civilian catastrophic release incidents (intentional or accidental) (NRC/COT, 2003). These values are called Acute Exposure Guideline Levels or "AEGLs" and include a range of concentration levels for different durations (minutes to hours) representing various levels of effect severity. Section 4.3.3 of this report describes AEGLs more fully and includes a comparison of these with inhalation toxicity estimates derived from the official DOD military interim-toxicity criteria.

The following sections are provided to clarify some of the specific nuances and objectives to be considered for Homeland Security applications as compared with those of the previously described for military deployments. Ultimately, the specific objectives and decisions are to be determined by appropriate non-military decision makers.

***Note:** The following section is included as a means to document the criteria that would be anticipated as most appropriate based on Homeland Security activities that USACHPPM has previously supported and coordinated with civil authorities.

3.7.1 Homeland Security/Civil Support Applications: Modeling and Simulation (Prediction and Planning)

Modeling applications for terrorist attacks in civilian environments are performed as a planning tool to identify areas that may be exposed and, in particular, to highlight where the more severe impacts are expected. In addition to providing general information as to overall extent of the potential threat, this information can be used to prioritize resources and procedures. This type of practice is routinely performed as part of emergency planning and response activities relating to TIC spills and accidental releases. Specific toxicity-based criteria (e.g., AEGLs) are used by Federal/state/local personnel who model chemical vapor plumes to establish general areas of hazard severity, determine evacuation and shelter-in-place areas, and identify areas needing evacuation and/or medical assistance. Specific casualty estimates are not part of typical civilian emergency evaluations as they are in military operational planning. However, in most contexts, civil authorities want to know the full extent of the problem (i.e., worst-case). This often includes identifying general areas where persons may die, areas where persons may have serious

effects requiring potential medical aid, and areas where persons will not be significantly affected but may have mild noticeable effects. "No effect" areas are also designated particularly when developing evacuation plans. Unlike military scenarios, civilian protective actions focus on evacuation and shelter-in-place for preventing exposures through use of protective decision criteria. Specific parameters to consider in the selection of toxicity criteria to be used in decisions regarding Homeland Security modeling and planning are described in Table 3-12.

Table 3-12. Toxicity Value Selection Factors for Homeland Security/Civil Support Modeling and Simulation (Prediction and Planning)

Key Objective(s):	- Identify areas of potential exposure; - Prioritize/rank exposure of concern
Associated hazard severity levels of concern:	- All
Address individual health threats	- Yes –assume diverse population and levels of susceptibility
Assessment type (qualitative risk ranking, numerical toxicity estimates)	- Qualitative assessment of general areas of varying severity - quantified toxicity estimates (for heterogeneous population) needed to bound different levels
Confidence required/Uncertainty acceptable?	- Incorporate/account for uncertainties

3.7.2 Homeland Security/Civil Support: Detection, Verification, and Decontamination

Detection systems used in Homeland Security and emergency response scenarios may include point and standoff devices/systems. Some equipment that is developed for or by the military is likely to be used in these scenarios, as the basic objectives are the same. Initial emergency response phase activities are similar to the immediate/operational phases of military decontamination – where the primary objective is to identify/contain/eliminate (decontaminate) major sources of agent contamination in order to save lives and minimize further casualties (see Table 3-10). The post-response consequence management phase will focus on thorough decontamination with verification for unlimited restriction (i.e., lower-bound negligible hazard range) to locations and equipment (such as would be required for military items returned to continental U.S. use as described in Table 3-10). Unlike in some military settings, point detectors and/or field verification methods that are not deemed to achieve adequate sensitivity can be supplemented with more readily available reach-back laboratory confirmation. Overall, decisions to allow unrestricted civilian reentry/use will require relatively high public confidence in the protective nature of decision criteria used to determine "how clean is clean enough." Specific parameters to consider in the selection of toxicity criteria to be used in decisions Homeland Security detection and decontamination goals are described in Table 3-13.

Table 3-13. Toxicity Value Selection Factors for Homeland Security/Civil Support Detection, Verification, and Decontamination	
Key Objective(s):	- Identify areas of potential exposure; - Prioritize/rank exposure of concern. - Verify decontamination effectiveness. - Determine reentry/ 'clean' criteria.
Associated hazard severity levels of concern:	- All - with focus on ability to detect levels below which significant health effects occur – or ideally below which any health effects would occur.
Address individual health threats/low-level exposures.	- Yes - ideally the lower bound of the Negligible range or based on protective civilian (heterogeneous population) toxicity values.
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified detection levels necessary – use of non-military values is advised.
Confidence required/Uncertainty acceptable?	- Incorporate/account for uncertainties.

3.7.3 Homeland Security/Civil Support: Protection

Civilian hazardous materials personnel, associated law enforcement, and rescue/response personnel will require PPE (e.g., clothing and respiratory protection) that performs adequately in CWA environments. Unlike in most deployment scenarios, reach-back/support capabilities to support such personnel (for change out, decontamination, new PPE) will be more readily available. In such scenarios, it is more feasible to have disposable equipment than in deployments. The goal of protection is similar. However, for civilian applications, it is presumed that added confidence and regulatory specifications are typically necessary to ensure the protective nature of PPE and minimize, if not eliminate, the potential for adverse health effects. Toxicity-based criteria used to test PPE breakthrough may be derived from interim-military toxicity criteria (for healthy 70-kg male military personnel), which may not adequately address potential health concerns associated with civilians using such equipment (e.g., diverse health status and ages, diverse ethnic origin, and females). Specific parameters to consider in the selection of toxicity criteria to be used in decisions Homeland Security protection goals are described in Table 3-14.

Table 3-14. Toxicity Value Selection Factors for Homeland Security/Civil Support Protection	
Key Objective(s):	- Prevent exposures resulting in effects.
Associated hazard severity levels of concern:	- All – design criteria should include testing against high (lethal) levels of exposure but the goal should be to provide an "internal environment" that would not result in health effects (e.g., lower bound, Negligible severity).
Address individual health threats/low-level exposures.	- Yes – ideally, the lower bound of the Negligible range based on protective toxicity values (for heterogeneous, non-deployed population).
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified "break-through" testing criteria needed to ascertain goal for maximum exposures acceptable with mask and ensembles – use of civilian values advised.
Confidence required/Uncertainty acceptable?	- Incorporate/account for uncertainties.

3.7.4 Homeland Security/Civil Support: Medical Interventions and/or Countermeasures

Use of medical pre-treatment for chemical warfare in a civilian sector is unlikely, with the possible exception of certain designated emergency responders. Therapeutic medical interventions may be required in the event of a CW incident and will likely use treatments similar to those employed by the military. New treatment interventions for civilian use may have to consider potential side effects relating to a more diverse population. Table 3-15 describes the specific parameters to consider in selecting the toxicity criteria to be used when making decisions dealing with Homeland Security medical countermeasure goals.

Table 3-15. Toxicity Value Selection Factors for Homeland Security/Civil Support Medical Intervention/Countermeasures	
Key Objective(s):	- Prevent fatalities/minimize severity. - Mitigate impacts of high-level exposures (lethal and incapacitating).
Associated hazard severity levels of concern:	- Testing criteria should include lethal levels; goal to reduce/eliminate health effects.
Address individual health threats.	- Minimize adverse side effects
Assessment type (qualitative risk ranking, numerical toxicity estimates).	- Quantified testing criteria needed to ascertain maximum effectiveness.
Confidence required/Uncertainty acceptable?	- Account for uncertainties.

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SECTION 4
TOXICITY ESTIMATES, EXTRAPOLATIONS, AND ADJUSTMENTS

The purpose of this section is threefold: (1) to describe the health effects associated with short-term (acute) exposures to the subject chemical warfare agents; (2) to present a current assessment of the DOD-certified interim-acute military toxicity data set; and (3) to provide an evaluation of various methods that may be used to select, extrapolate, and adjust values from the DOD interim-acute military data set to provide the range of criteria needed to address military operational applications previously described in Section 3.

Of particular focus is the estimation of the upper and lower bounds of the Negligible severity range that represents low-level exposures (as described in Section 1.3 and Section 2). The lower-bound estimates include consideration of susceptibility factors within a heterogeneous population and are considered reasonable PTEs that represent protective criteria below which no clinically significant effects are anticipated even among a heterogeneous population.

***NOTE:** Because this report pertains to scenarios involving rare, infrequent, often single exposures extending from minutes to a few hours, this section focuses on the toxicity and health effects associated with short-term, relatively brief (acute) exposure durations (as opposed to repeated, long-term (chronic) exposure durations). While some scenarios could theoretically extend beyond a few to several hours, the primary focus includes the more probable limited exposure durations of minutes to multiple (up to 24) hours.

4.1 SUMMARY OF HEALTH EFFECTS FROM SHORT-TERM (ACUTE) CHEMICAL WARFARE EXPOSURE

4.1.1 Sulfur Mustard

4.1.1.1 Acute (Latent) Effects from Single Exposures to Sulfur Mustard

HD is a vesicant (blistering) agent. The effects of HD are latent and do not develop until after a post-exposure period of hours to days. Warm moist tissues such as the eye, respiratory tract/lung, and delicate skin areas are particularly vulnerable to characteristic cell damage and cell death. Toxicological effects are local at the point of contact with the eye and skin and often begin to appear (depending on exposure concentrations) within approximately 2-3 hours post-exposure. The earliest manifestation is usually eye reddening and conjunctivitis. Skin exposure can be followed by an itching rash, which may progress to swelling and erythema, and (sometimes large) blisters (IOM, 1993; Papirmeister, et .al., 1991).

At very high levels, systemic effects such as bone marrow depression (resulting in leukopenia and anemia) can also occur. Exposures generating these conditions usually produce visible injuries such as skin blisters and temporary blindness in the hours following initial exposure. Skin blisters are relatively painless for several days, but after 5-6 days, the pain becomes severe

upon exposure to air or on contact; sensitivity of the blistered area can persist for weeks. As exposure to HD also results in immunosuppression, blistered or ulcerated areas can become infected. The principal cause of mortality in the first few days to weeks after exposure to large concentrations of HD is damage to the respiratory tract, which involves acute edema, inflammation, and destruction of the airway epithelial lining. Infection of the respiratory tract resulting in bronchopneumonia is a common complication.

4.1.1.2 Delayed, Long-Term, and/or Permanent Effects from Sulfur Mustard

Individuals exposed to doses of HD sufficiently high to cause skin lesions often suffer from long-term or permanent skin abnormalities (e.g., increased pigmentation and depigmentation, chronic ulceration, scar formation, and skin cancer) even after the primary lesions have healed. Exposures at these levels can also result in later development of respiratory conditions such as chronic bronchitis and cancers of the upper respiratory tract. Some individuals exposed to HD concentrations that are damaging to the eyes are more susceptible to delayed recurrent keratitis and corneal ulceration. These injurious exposures have occurred on the battlefield (e.g., World War I; Iran-Iraq conflict of 1980-1988) and in war gas factories with poor industrial hygiene practices (i.e., Japan, 1929-1945) (IOM, 1993).

4.1.1.3 Non-Clinical Effects Associated with Sulfur Mustard

There are no data documenting the occurrence of non-clinical effects in individuals exposed to vapor concentration of HD below those producing noticeable adverse effects such as mild erythema (i.e., skin inflammation).

4.1.2 Nerve Agents

4.1.2.1 Acute Effects from Single Exposures to Nerve Agents

Nerve agents are so named because of their anti-cholinesterase properties and subsequent adverse effects on smooth and skeletal muscle function and the central nervous system. Toxic effects, which occur by all routes of exposure, can appear within seconds or minutes post-exposure, and depending on the exposure level and duration, may include one or more of the following: miosis (i.e., contraction of the pupils of the eye, with subsequent decrease in pupil diameter); conjunctival congestion; eye pain; distorted vision; rhinorrhea; salivation; excessive sweating; bronchoconstriction; increased bronchial secretions; cough; dyspnea; nausea; vomiting; diarrhea; abdominal pain; muscle fasciculations; twitching; weakness; alterations in heart rate and blood pressure; loss of reflexes; slurred speech; ataxia; paralysis; loss of consciousness; convulsions; coma; and death (Sidell, 1992). Minimal effects can be limited to miosis, tightness of the chest, rhinorrhea, and dyspnea. The presence of rhinorrhea can be indicative of inhalation exposure and/or development of systemic effects, while only miosis, in the absence of other signs or symptoms, is a local effect on the pupillary muscles of the eye. As a consequence, miosis is considered a sensitive indicator of direct vapor exposure (NRC, 2003).

4.1.2.2 Delayed, Long-Term, and/or Permanent Effects from Nerve Agents

Laboratory animals protected by large doses of antidotes and then exposed to multiple lethal concentrations of G-agents can exhibit delayed neurotoxic effects (e.g., distal neuropathy, ataxia and paralysis, referred to as organophosphate induced delayed neuropathy or OPIDN). OPIDN usually appears several days to several weeks after an acute exposure. The potential for OPIDN occurring in humans exposed to any of the G-series agents would only be a concern for those individuals surviving a single exposure to agent concentrations greater than $30 \times LD_{50}$. Animal data for VX indicates that VX does not induce OPIDN, even at multiple LD_{50} concentrations (see Munro, et. al., 1994 for review and NRC, 2003).

For non-lethal exposures, small but measurable single fibre electromyographic (SFEMG) changes in the forearm muscle of human subjects have been observed following experimental GB vapor exposures. These effects were detected until 15 months post- exposure, which may constitute a long-term effect; however, these effects are observable only in a laboratory setting, are subclinical, and are fully reversible (Baker and Sedgwick, 1996). Such subclinical neurological changes (from single, short-term exposures) have not been associated with any delayed, long-lasting, or permanent clinical or health effects. A computer analysis of electroencephalograms (EEGs), recorded one year or more after the last exposure to GB had occurred, indicated potential EEG differences that were not confirmed by neurological examination. Therefore, these EEG amplitude differences were considered clinically insignificant (Duffy, et. al., 1979; Duffy and Burchfiel, 1980).

4.1.2.3 Non-Clinical Effects Associated with Nerve Agents

Following absorption into the body, nerve agents bind with and inhibit the activity of cholinesterases (ChE) that are present in the blood and other tissues. Blood ChE activity depression by itself is not considered an adverse effect but (particularly red blood cell cholinesterase (RBC-ChE)) has been used as biomarker of exposure or a monitor of recovery. Typically, RBC-ChE activity depression must be at 20-30 percent before health concerns are raised (USEPA, 2000). However, there is significant biological variation in the normal (baseline) levels of ChE activity in different individuals, so assessment of ChE activity depression should consider change relative to an individual's normal baseline enzyme activity levels over time. Also, other substances, physiological conditions, medications, or hormonal levels can alter ChE activity. Use of blood ChE activity as a biomarker of exposure, therefore, should be used in conjunction with knowledge of these considerations.

As previously indicated, non-clinical effects attributed to low-level nerve agent exposure include SFEMG changes. These have not been attributed to identifiable adverse health impacts, though their significance is still being investigated. While a recent GB animal (rat) study (Henderson, et. al., 2002) identifies neurological effects of concern after several repeated exposures, the single exposures conducted in the study were associated only with minimal (7 and 11 percent) inhibition of RBC-ChE activity, and they "did not alter body weight, breathing patterns, routine brain histopathology, or apoptosis in brain cells."

4.2 INDIVIDUAL AND POPULATION SUSCEPTIBILITIES

The variation in human response is typically considered when estimating toxicity of a chemical. Depending on the type of chemical, its mechanism, and target organs, there are potentially vast differences in the degree of response among persons from a heterogeneous population of mixed gender, age, ethnic and genetic make-up, and health status. However, the variation among humans may be minimal for some chemicals, mechanisms, or effects. Such variability needs to be addressed on a chemical-specific basis. It is important to keep in mind that the composition of the modern deployed force more closely reflects the diversity of the general population (except for the obvious absence of children and elders); previously assumed norms (e.g., "70-kg male") regarding uniformity of response are no longer valid. To address this human intraspecies variation, some toxicity estimates and health guidelines or standards are based on studies involving a more susceptible "subpopulation" (e.g., as asthmatics for certain irritants). Where such studies and data are not available, a standard approach for developing toxicity criteria for a heterogeneous population is the application of an uncertainty factor (UF). The assumption is that a toxicity value derived from limited data, if reduced by a UF (a default factor of 10 or, if less variability is justified by data, an alternate UF value such as 2, 3, or 5) will result in criteria that will be reasonably protective for a heterogeneous (mixed) population. If data suggest minimal or no identifiable subpopulations of greater susceptibility, then the UF would be established as a value of 1.

The following paragraphs describe identifiable susceptibility factors and subpopulations that would be expected to have greater susceptibility to the effects of chemical warfare agents.

4.2.1 Susceptibility to Sulfur Mustard

The most susceptible target organ for HD exposure is the eye. Human and animal data indicate that direct effects on the eye (e.g., watering, reddening, and swelling of the eyelids taking place 2-3 hours following exposure) do not vary much between individuals. Furthermore, animal data indicate that there is no significant difference in vesicant-induced skin damage between males and females; nor do there appear to be substantial differences in cutaneous response on the basis of race (e.g., dark versus light skin) (IOM, 1993; Wormser, et. al., 2002). There is also no evidence of individual or population differences in respiratory tract tissue effects following exposure to HD, though some potential for increased susceptibility to those with existing respiratory impairments (which may be more frequent in an aging population) has been suggested. Of greater importance, data from battlefield casualties have demonstrated the significance of variation in susceptibility in different body regions (which is further enhanced by heat and moisture). Appendix E, Tables E-1 and E-2, summarize casualty data relating to different body regions.

In summary, the key conclusions regarding HD susceptibility factors include—

- Susceptibility to effects of direct HD exposure to the eye is not significantly influenced by individual or subpopulation factors. An instraspecies adjustment factor (UF) of 1 or 3 would be reasonable to accommodate for a mixed population for this route.

- Susceptibility to HD from inhalation exposure may be slightly greater to those with existing respiratory illness (such as bronchitis), though no data have definitely shown this. The mechanism of HD action (alkylating cell poison) does not result in much tissue injury variation between or among individuals or populations. A UF of 3 for intraspecies variability would be reasonable to accommodate a mixed population for this route.

- Body region variation (in addition to hot, humid environmental conditions) is considered the most significant aspect of susceptibility for percutaneous chemical warfare exposures (NRC/BAST, 1997). A UF of 1 for instraspecies variability would be reasonable to accommodate a mixed population for this route; however, it is important to note that—

    - The identification of specific body regions (e.g., groin, scrotal area) as the most susceptible to percutaneous exposure is supported by casualty data.

    - The location (i.e., body region) at which effects occur will dictate degree of incapacitation in that the characteristic burns and blisters following HD exposure cause greater and more rapid debilitation when they develop at susceptible body regions (e.g., groin, scrotal area, head and neck, armpits (Smith, 2002; Sidell, et. al., 1997).

4.2.2 Susceptibility to Nerve Agents

Nerve agents exert their toxic effects by interaction and inhibition of enzymes that control nerve and nerve-muscle function throughout the body. The severity of a nerve agent exposure depends on the amount and rate at which the agent enters the body, the rate and extent of detoxification that occurs, and the target organs affected.

The most sensitive organ to nerve agent vapor exposures is the eye, where various degrees of miosis can occur as a consequence of pupillary muscle contraction. When caused by direct agent vapor contact, this effect is local and can occur in the absence of other effects or ChE activity inhibition. The variation in individual or subpopulation susceptibility to miosis is considered minimal across multiple species (Mioduszewski, et. al., 2002a and 2002b; van Helden, 2001 and

2002; Harvey, 1952; Johns, 1952). Other literature describing the potential distribution of susceptible subpopulations was also considered (Crosier, 2003).

For percutaneous exposure to nerve agents, the degree of physiological effect depends largely on regional body variation in skin thickness, etc., as discussed for HD. The greater susceptibility of regions (such as the groin, scrotal area, head and neck, and armpits) has been documented on the basis of operational and laboratory data as well as literature on exposures to commercial organophosphate (OP) pesticides. (Sim and Stubbs, 1960; Sim, 1962; and Duncan, et. al., 2002).

For systemic exposures to nerve agents, detoxification is a critical factor in determining magnitude of agent effects. Detoxification is largely a function of the presence of various enzymes in the blood and other tissues, which can combine with and deactivate the agent before it reaches the target organ. Slower rates of detoxification and resulting enhanced susceptibility have been correlated with gender, age, physiological state, and genetic predisposition. Specifically, the following types of factors or conditions have been specifically associated with increased susceptibility to anti-cholinesterases, such as nerve agents—

- Several studies indicate that plasma and RBC-ChE activity are significantly lower in women than in men (reviewed in Hayes, 1982; Wills, 1972); data also show that female rats are statistically more susceptible (by approximately a factor of 2) than males, based on the effective concentration 50 percent (EC_{50}) for miosis or lethality following GB vapor exposure. (Mioduszewski, et. al., 2000, 2001, 2002a and 2002b; Anthony, et. al., 2002).

- Plasma-ChE activity is often depressed in pregnant women and individuals with liver disease or dysfunction, heart disease, allergic conditions and neoplasms (Wills, 1972).

- A small, human subpopulation (estimated to be approximately 3 percent) possesses certain genetically determined low activity levels of plasma ChE and may be unusually sensitive to some anti-cholinesterase compounds (Morgan, 1989).

- Individuals and subpopulations also have different levels (up to 13-fold between individuals) of A-esterases (paraoxonase/arylesterase) in the blood and liver as a result of genetic factors. Those with lower levels would presumably detoxify agent at a slower rate (Furlong, 2002).

- Certain ethnic groups (e.g., Black Americans, Japanese, and other Oriental groups) are known to contain individuals expressing enzyme forms that have low-hydrolyzing activity. Such persons could be more susceptible to OP anti-cholinesterase poisoning (some sources are: Yamasaki, et. al., 1997; Morgan, 1989; Davies, et. al., 1996; Furlong, et. al., 2002; Chanda, et. al., 2002; and Costa, et. al., 2003).

In summary, the key conclusions regarding nerve agent susceptibility factors include—

- Susceptibility to direct vapor nerve agent *eye* exposure and the local effect of miosis are not thought to be significantly influenced by individual or subpopulation factors. An adjustment factor (UF) of 3-10 would be protective to accommodate a mixed population for this route and effect.
- Susceptibility to systemic nerve agent effects from *inhalation* exposure is greater for those with slower detoxification rates due to presence of genetic variation, physiological state, etc. A UF of 10 would be reasonable to accommodate a mixed population for this route given data that do not specifically account for such variability.
- Body region variation (in addition to hot, humid environmental conditions) is considered the most significant aspect of susceptibility for *percutaneous* exposures, as rate of absorption is dependent on skin thickness/anatomical differences and amount of sweat. A UF of 1 would be reasonable to accommodate for a mixed population for this route.

4.3 OVERVIEW OF IDA CHEMICAL WARFARE AGENT TOXICITY ESTIMATES

4.3.1 IDA Interim-Certified Military "Baseline" Toxicity Estimates

As described in Section 1 of this report, in December 2001 the DATSD-CBD endorsed a policy that provides interim-certified CWA acute toxicity values for application to threat and concept of operations planning, active and passive defense, counter-force operations, and other military needs where the impact of chemical weapon use is critical (DATSD-CBD, 2001). These interim-toxicity values are documented in the IDA report (see Appendix B of this report and Grotte and Yang, 2001).

4.3.1.1 Background and Basis for the IDA Interim-Certified Toxicity Estimates

The toxicity estimates in the IDA report summarize the consensus of a 1998 Joint NBC Board workshop that represented the military chemical defense community, the medical community, the analytical community, the three services, the Joint Service Integration Group, and the Joint Service Materiel Group. During this workshop, members evaluated official existing military toxicity estimates presented in FM 3-9 by comparing them with proposed military toxicity estimates for nerve and mustard agents that had been established in the Reutter-Wade report (R-W, 1994). The workshop review included comparison of these estimates along with recommendations provided by a 1997 National Research Council Committee on Toxicology (NRC/COT) (NRC/COT, 1997) report. There was general consensus that many of the values in FM 3-9 were not sufficiently conservative (low). However, not all of the proposed Reutter-Wade or NRC/COT recommendations were agreed upon. Therefore, some of the IDA toxicity estimates are different than those initially proposed by the Reutter-Wade report, and many do not reflect NRC/COT (1997) recommendations. The IDA report does not completely document the

scientific rationale for not accepting various NRC/COT (1997) recommendations but does indicate that the workshop members considered that there was little to be gained from modifying certain toxicity estimations given the likelihood that estimates would change as more research was conducted. As a result, the IDA report recommended the consensus values as "interim" estimates pending findings of future research.

4.3.1.2 Description of the Military (DATSD-CBD) Interim-Certified Toxicity Estimates

The acute interim-certified toxicity estimates provided by the IDA report include two values: a baseline median population cumulative exposure and a probit slope (see Glossary). Median toxicity estimates are provided for lethality (LCt_{50} values for inhalation and percutaneous vapor exposures); LD_{50} values for percutaneous liquid exposures), as well as for "mild," "threshold," and "severe" effects (ECt_{50} values for mild effects from inhalation or ocular exposures; ECt_{50} values for threshold effects from percutaneous vapor exposures; ECt_{50} values for severe effects from inhalation, ocular and percutaneous vapor exposures, and ED_{50} values for severe effects from percutaneous liquid exposures). These estimates (referred to as the IDA-toxicity values) were derived for 70 kg healthy male soldiers. For HD, separate sets of percutaneous vapor toxicity estimates are given for moderate and hot ambient temperatures.

All estimates for inhalation and ocular exposures are expressed in terms of *Ct* (concentration in milligram per cubic meter (mg/m^3) multiplied by exposure duration in minutes; *Ct* units in mg-min/m^3) and are reported for 2-min exposures. Inhalation exposure estimates assume a minute volume of 15 liters. Percutaneous vapor (and small particle aerosol) estimates are reported for 30-min exposures for individuals without clothing. For the nerve agents, the percutaneous vapor estimates are for masked soldiers with eye protection. Percutaneous liquid estimates are for the total applied dose (in mgs) to a 70-kg man, assuming complete percutaneous absorption.

4.3.1.3 IDA Limitations and Outstanding Issues

The median effect values summarized in the IDA report have important uses. However, no one set of values can fit all applications, and the report acknowledges limitations, as follows:

- Data from different studies were grouped or combined to estimate certain endpoint *Cts* as opposed to the use of a single study with defined endpoints.

- Original data on which the numbers are based are not available to determine the confidence limits of the values (because estimates were derived from grouped data, some of which are classified).

- Values are for median effect levels (e.g., ECt_{50}, LCt_{50}) and specific limited exposure durations only. No time extrapolation method is specified, though it is noted that direct linear extrapolation (Haber's Law or $C \times t = k$) is probably not appropriate.

- ECt_{50} (severe effect) values represent effects that are too severe for many current military applications and scenarios under consideration.

- ECt_{50} values are effect levels for 50 percent of the population and, therefore, may not be protective for a large segment of the exposed population.

- The term "threshold" for percutaneous vapor exposures is not well defined. For nerve agents, percutaneous vapor threshold is slight ChE inhibition; for HD, percutaneous vapor threshold is the midpoint of the dosage range where effects just begin to occur.

- Estimates do not address uncertainties associated with the median values or the probit slopes despite the wide range in quality and degree of confidence for each chemical.

- Probit slopes allow expected effects to be calculated at lower and higher percentile values than the medians using standard methods, but extrapolations below the 16^{th} percentile and above the 84^{th} have low reliability.

- For percutaneous toxicity estimates, it is unclear whether susceptible body regions have been adequately considered.

- Estimates are designed for 70-kg male soldiers and are specifically not intended for application to scenarios involving female military personnel, soldiers representing certain ethnic groups, soldiers possessing certain physiologies (e.g., liver conditions or some allergies), or the general population. (Potential reduction of the estimates by factors of 2 and 10 to down-adjust exposures for the general population or sensitive subgroups were mentioned, but a factor was not specifically recommended.)

Furthermore, neither the DASTD-CBD nor the IDA report provide specific guidance regarding—

- The process for selecting or deriving toxicity values for specific operational applications.

- The operational significance of various toxicity range estimates to various applications.

- The applicability of the values to current FHP requirements.

- The process whereby new toxicological research will be factored into operational considerations.

In addition, the DASTD-CBD report does not take into consideration the AEGLs that have recently been judged as scientifically valid by the NRC and published by the National Academy Press (NRC/COT, 2003).

4.3.2 Third Party Review of Proposed Military Toxicity Values

The NRC/COT Subcommittee on Toxicity Values for Selected Chemical Warfare Agents (NRC/COT, 1997) evaluated the scientific validity of the 1994 proposed Reutter-Wade military toxicity estimates. The NRC/COT report accepted the log-probit analysis used to derive the military toxicity estimates (LCt_{50} and ECt_{50} values) as a reasonable approach. The NRC/COT noted, however, that there is a level of uncertainty associated with each median value that depends on the quality of the original experimental data from which the value is based. According to the NRC/COT, the reported confidence limits on the toxicity estimates were often a factor of 2, meaning that they could vary from $ECt_{50}/2$ to $2 \times ECt_{50}$. However, confidence limits for each individual median value were not given by NRC/COT. Because the Reutter-Wade report (R-W, 1994) remains secret, the confidence limits for specific agents cannot be readily determined. In addition, the NRC/COT review (NRC/COT, 1997) states, "the uncertainty of the exposure estimates might be as much as a factor of 10." This same uncertainty carries over to all extrapolated probit values derived from those presented in the IDA report.

The NRC/COT also made specific recommendations on each proposed median toxicity estimate citing whether the value was a valid estimate, whether the value should be raised, or whether the value should be lowered. The NRC/COT did not provide specific alternative estimate values. As indicated, the 1998 IDA workshop resulted in some changes to the original Reutter-Wade proposed estimates based on the NRC/COT review, but the workshop did not accept all the recommendations. In addition, the IDA workshop established estimates for severe percutaneous vapor exposures. Table 4-1 summarizes the differences between the NRC/COT recommendations and the IDA values.

It is of some concern that the majority of the NRC recommendations were not addressed, particularly in that many of the unaddressed recommendations were to lower the values proposed in the original Reutter-Wade report (R-W, 1994). For a few estimates, instead of lowering the original proposed value, the estimate was ultimately raised in the IDA report. However, the IDA consensus considered that the implication of making significant changes was too great given the uncertainties and potential of future additional research data.

Table 4-1. NRC/COT 1997 Recommendations Not Reflected in the 2001 IDA Acute CWA Toxicity Estimates (see footnote[a] for units)

Agent	Parameter	Route of Entry	R-W estimate[b]	NRC/COT 1997[c] recommendation	IDA 2001[d] (interim-military estimate)
GA	LCt50	inh. vapor	70	Lower estimate	70
	ECt50-severe	perc. vapor	No estimate	Not evaluated	12000
	LD50	perc. liquid	1500	Lower estimate	1500
	ED50 -severe	perc. liquid	880	Lower estimate	900
GB	LCt50	perc. vapor	10,000	Valid estimate	12,000
	LCt50	inh. vapor	35	Lower estimate	35
	ECt50-severe	perc. vapor	No estimate	Not evaluated	8000
	ECt50-severe	inh. vapor	25	Lower estimate	25
GD	LCt50	perc. vapor	2500	Valid estimate	3000
	LCt50	inh. vapor	35	Lower estimate	35
	ECt50-severe	perc. vapor	No estimate	Not evaluated	2000
	ECt50-severe	inh. vapor	25	Lower estimate	25
GF	LCt50	perc. vapor	2500	Interim estimate	3000
	LCt50	inh. vapor	35	Lower estimate	35
	ECt50-severe	perc. vapor	No estimate	Not evaluated	2000
	ECt50-severe	inh. vapor	25	Lower estimate	25
VX	LCt50	inh. vapor	15	Lower estimate	15
	ECt50-mild	inh. vapor	0.09	Valid estimate	0.1
	LD50	perc. liquid	5	Lower estimate	5
HD	LCt50	perc. vapor	5000	Lower estimate	10,000
	LCt50	inh. vapor	900	Valid estimate	1000

[a] Percutaneous and inhalation vapor estimates are in units of mg-min/m^3; percutaneous liquid estimates are mg per 70-kg man.

[b] Reutter and Wade, 1994, non-classified summary table (Table 1, *Summary of Existing and Recommended Estimates (U)*).

[c] NRC/COT, 1997.

[d] Grotte and Yang, 2001 (IDA report).

4.3.3 Relationship to Other Toxicity-Based Criteria

In addition to the military acute toxicity estimates, exposure guidelines for nerve agents and HD have been established by several organizations. These exposure guidelines and their relevance to the rare, short-term exposure scenarios focused on in this report are summarized below—

- Department of the Army Pamphlet (DA Pam) 40-8, *Occupational Health Guidelines for the Evaluation and Control of Occupational Exposures to Nerve Agents GA, GB, GD, GF and VX*, (DA draft, February 2003a) and DA Pam 40-173, *Occupational Health Guidelines for the Evaluation and Control of Occupational Exposures to Mustard Agents H, HD, and HT*, (DA draft, February 2003b) were staffed through the Army with proposed changes to some of the

previously established airborne exposure limits (AELs) for agent workers as well as for potential chronic exposures to the general public (for evaluating incinerator emissions). The AELs include the worker Immediately Dangerous to Life or Health (IDLH) level (for determining environments requiring fully encapsulated, self-contained breathing apparatus), worker population limit (WPL) (daily 8-hour time-weighted averages (TWAs) over several work years), and the general population limit (GPL) (for daily 24-hr exposures over several years). The addition of new worker short-term exposure limits (STELs) were also proposed in the draft DA Pam 40-8 and the draft DA Pam 40-173 (DA, draft February 2003a and 2003b). The Centers for Disease Control and Prevention (CDC) completed evaluation of the proposed Army changes and published their own recommendations for AELs for certain nerve agents and sulfur mustard, including those for the STELs and IDLH values (Federal Register, 2003 and 2004). At the time of this publication, the Army is considering implementing the CDC criteria in place of the proposed Army values. The Army AELs for nerve and mustard agents are compared with the new proposed Army values and the new final CDC values in Appendix F (Table F-1). While the WPL and GPL have no application to the rare/single short-term exposure scenarios being addressed by this report, the IDLH and/or STEL values may have some applications even though they are designed for industrial, work-related situations.

- *Acute Exposure Guideline Levels* have also been specifically derived for the chemical warfare nerve agents (GA, GB, GD, GF, VX) and HD (NRC/COT, 2003). These are presented in Appendix F (Table F-2). AEGLs generally indicate the concentrations of a chemical in air above which different types of health effects could begin to occur in unprotected civilian populations after single, one-time exposures lasting minutes to hours. AEGLs are designated for hundreds of TICs and are to be used by Federal and state agencies to aid in the development of emergency preparedness plans, as well as to prioritize response actions in the event of a chemical release from an accident or intentional terrorist attack. The Army and the Federal Emergency Management Agency (FEMA) have officially adopted the CWA AEGL values as the toxicity criteria to be used by the Chemical Stockpile Emergency Preparedness Program (CSEPP) community for the purpose of prioritizing resources and activities associated with chemical agent release (CSEPP, 2003). Several states have since adopted AEGL levels as primary emergency planning guidelines for use in such areas as designating downwind hazard distances. The AEGLs are the most appropriate criteria for most Homeland Security applications. The CWA AEGLs are derived from evaluation of the non-classified historical acute inhalation CWA studies included in the IDA inhalation estimates, along with a few new well-conducted animal inhalation studies (Mioduskewski, et. al., 2000, 2001, 2002a and 2002b; Kumar et. al., 1998) and even a low-level human exposure study (Baker and Sedgewick, 1996). The AEGL derivation approach involves selection of a single critical study and endpoint (which is supported by other studies) to estimate an effect level. This estimate is adjusted with UFs to account for animal to human extrapolation and human variation in susceptibility. In addition, for chemicals that have few agent-specific studies (such as in the case of VX), an additional adjustment is incorporated to accommodate sparse data. AEGLs include three categories for varying levels of health effect severity (i.e., AEGLs 1, 2, and 3) for each of five time durations (10 min, 30 min, 1 hr, 4 hr, and

8 hr) reflecting a compound's relative dose-response and concentration-time relationship. AEGLs represent civilian "population thresholds" for the following:

- AEGL 1: minimal transient, non-impairing effects.
- AEGL 2: effects that are either long lasting, permanent, or escape-impairing.
- AEGL 3: effects that are incapacitating and could lead to death without medical intervention.

- The time extrapolation relationship is referred to as the ten-Berge model or $C^n \times t = effect\ k$ (ten Berge, et. al., 1986) versus Haber's Law $C \times t = k$. For nerve agents an n value of "2" was derived from recently published studies (Mioduszewski, et. al., 2002a and 2002b). Time extrapolation for HD is considered linear ($n = 1$) for all AEGL estimates except the AEGL 3 values for 10 min and 30 min (NRC/COT, 2003). The operational community has expressed concerns that the AEGLs might be overly protective for military uses because they are derived for civilians (i.e., heterogeneous populations) and have safety factors built in to account for scientific uncertainties.

4.4 GENERAL SUMMARY OF THE IDA REPORT

The IDA toxicity values represent the estimated dosages (*Ct*) that would produce various health effects (e.g., death, severe effects, or mild effects) in 50 percent of "healthy male soldiers" who are exposed to a CWA for a brief period of time. The IDA 50 percentile estimates have not been adjusted for uncertainties associated with the median values or the probit slopes despite the acknowledged and wide range in data quality and degree of confidence for each CWA.

The probit-slope values associated with the IDA median can be used to statistically extrapolate these median values to determine dosage estimates associated with other percentages of population effects (e.g., LCt_{16} = 16 percent deaths). This probit extrapolation is a standard scientific procedure which can be used to provide a range of various toxicity values. However, probit extrapolation is only the first of several mathematical steps that are necessary to provide the types of toxicity-based values needed for so many military applications. Most applications require concentration values as opposed to *Cts*. The method to convert the IDA-based *Cts* involves the selection of the exposure duration of concern, and then the selection of an appropriate time extrapolation model. Finally, the need (as described in Section 1.3) to consider the increased susceptibility of people within military who differ in age, genetic composition and ethnicity, gender, and physiological condition must be considered and factored in as appropriate. Appropriate protective values can be derived by applying adjustments or UFs to the IDA-based values. Specifically, the standard probit-statistical techniques can be used to estimate the exposure levels that would cause effects to low percentiles of healthy 70-kg military males; the values then converted to concentrations and adjusted with UFs that can reasonably address the potential variation in human response. The use of the military-specific IDA values along with

these specific extrapolation procedures is in line with recommendations made by the NRC (NRC/COT, 2004) to update and improve MEGs currently cited in USACHPPM TG 230 (USACHPPM, 2004).

***NOTE:** Though the estimates can be extrapolated to address potential susceptible subpopulations that could potentially accommodate those found in even a civilian population, these values are still not designed for civilian applications. Instead, the AEGLs and other values (as described in Section 4.3.3) are considered more appropriate for Homeland Security applications.

The following sections describe and evaluate specific methods for the time extrapolations and adjustments for applying the IDA values to military deployment applications.

4.5 METHODS FOR EXTRAPOLATION AND ADJUSTMENT OF MILITARY ESTIMATES

Though the NRC/COT (1997) considered log-probit analysis to be a reasonable approach for evaluating the toxicity estimates for these agents, they note the lack of confidence intervals and degree of uncertainty. IDA also notes that although the probit slopes may be used to estimate population effects lower than (or greater than) the 50 percent median values, the statistical uncertainty is particularly great for extrapolation beyond one standard deviation (e.g., less than EC_{16} or greater than EC_{84}). This is particularly problematic for the many applications (described in Section 3) that require an estimate representing a minimal effect on the exposed population or PTE). But the IDA report also acknowledges that "probit-based methodologies may not be suitable for all cases" and specifically points out that other candidate methodologies should be explored.

Therefore, in keeping with the guidance from these earlier evaluations of the Reutter-Wade assessment and logic (R-W, 1994), this report evaluates various approaches to derive PTE in addition to log-probit analysis. These alternate approaches are based, in part, on procedures used by regulatory and advisory bodies responsible for developing toxicity values for other highly toxic chemicals such as phosgene, chlorine, etc. (i.e., the USEPA and the NRC/COT).

4.5.1 Estimating ECt_{01} and ECt_{16} Effect Levels

Using the ECt_{50} values given in the IDA report as a starting point, the ECt_{01} and ECt_{16} values can be estimated using standard statistical methods. **Statistically, values below the 16th percentile have low reliability**, but such values are nevertheless useful for comparative purposes. An approximation of the ECt_{01} values might be obtained in several other ways: (1) by adjusting the ECt_{50} for threshold or mild effects by the same proportional difference exhibited by ECt_{50} values for severe and threshold or mild effects; (2) by applying a UF to the ECt_{50} values; or (3) by adjusting the ECt_{50} threshold or mild values by the same proportional amount used to estimate an LCt_{01} from an LCt_{50}. Each of these approaches is discussed in more detail below.

- ECt_{01} and ECt_{16} by Cumulative Exposure (Log-probit) Extrapolation. The log-probit extrapolation method assumes that the density distribution among exposed individuals for a specific endpoint (i.e., death, severe incapacitation, or mild effects) is described by a log-normal distribution (NRC/COT, 1997). The ECt_{50} is the cumulative exposure (i.e., concentration times exposure duration) that is estimated to cause an effect in 50 percent of the population. As a means of estimating the 1st and 16th percentiles (ECt_{01} and ECt_{16}), standard statistical methods have been employed to incorporate IDA report probit-slope values for extrapolation from the IDA median values to percentile values at the lower end of the log-normal distribution curve. It is acknowledged that statistically, values below the 16th percentile have low reliability, but such values are nevertheless useful for comparative purposes. The probit-analysis method is described in more detail in Appendix E, E.1.

- ECt_{01} Approximation by Ratio of ECt_{50} Severe and Threshold or Mild Estimates. Another approach for estimating ECt_{01} values assumes that the ratio between the median IDA toxicity values (ECt_{50}) for severe effects and threshold/mild effects is both compound- and endpoint-specific. Thus, if this same ratio is applied to the threshold or mild effects value, the resulting estimate will correspond to an estimated ECt_{01} for threshold or mild effects—

$$\frac{ECt_{50}(severe)}{ECt_{50}(threshold/mild)} = \frac{ECt_{50}(threshold/mild)}{Estimated\ ECt_{01}(threshold/mild)}$$

$$therefore:$$

$$Estimated\ ECt_{01}(threshold/mild) = ECt_{50}(threshold/mild) \times \frac{ECt_{50}(threshold/mild)}{ECt_{50}(severe)}$$

Application of this approach to the ECt_{50} values for the CWA toxicity estimates in the IDA report results in the ratios summarized in Appendix E, Table E-3. This is an exploratory approach that has not been used in previous published studies; the results are used for comparative purposes only.

- ECt_{01} Approximation by Uncertainty Factor Application**.** Another method that can be used to estimate ECt_{01} values for threshold or mild effects is to apply a standard default UF of 10 to the ECt_{50} value for threshold or mild effects from the IDA report. The USEPA uses a similar UF approach in deriving oral Reference Doses (RfDs) and inhalation Reference Concentrations (RfCs). For deriving RfDs and RfCs, a UF of 10 is applied to the experimentally derived lowest effect level to estimate a level above which effects would be unlikely to occur (USEPA, 1989; 1994). If an ECt_{50} for mild or threshold effects is considered to be equivalent to a lowest-adverse effect level, then application of a UF of 10 could theoretically reduce the value to an estimated ECt_{01}.

The use of UFs for estimating percutaneous toxicity endpoints is not well characterized, and the literature review performed during the present analysis could find no precedent for such a procedure.

- ECt_{01} Approximation by the Lethality Ratio. According to the NRC/COT (2001), an LC_{01} can be approximated from an experimentally derived LC_{50} when certain parameters can be met by the experimental data (i.e., all experimental exposure levels should have caused some lethality); there is a steep dose-response curve; and data characterizing response at the lower part of the dose-response curve are available for examination. If these conditions can be met, then the LC_{50} can be divided by a single specific factor (typically a factor of "3", based on average factors documented in the experimental literature for inhalation toxicity experiments, with a 90^{th} percentile of 2.9 and a 95^{th} percentile of 3.5, and a range of 1.1 to 6.5 (NRC/COT, 2001)). However, the NRC has only used this method for a lethality endpoint and only for inhalation vapor exposures. This method has no established biological or statistical basis, and no precedent for the specific application to percutaneous or non-lethal inhalation exposure assessment. However, despite the considerable uncertainty concerning its validity, this approach does, to some degree, reflect agent- and endpoint-specificity, which makes it useful for comparative purposes only.

4.5.2 Adjustments for Heterogeneous Populations

As previously indicated in Section 4.2, there are various physiological factors that can result in increased susceptibility to the biological mechanisms by which these agents induce their effect. The IDA report (Grotte and Yang, 2001) and the NRC/COT (1997) report both state that military toxicity estimates are only for healthy 70-kg male military personnel and should not be used for civilians or scenarios involving susceptible subpopulations to include females, certain ethnic groups, and/or persons possessing certain physiologies (e.g., liver conditions, some allergies, respiratory illness, etc.). Particularly for protective applications in which a PTE is desired, some adjustment to the IDA "male military" estimates described above is warranted. The UF values described in Section 4.2 for human (intraspecies) variation for each agent are summarized below.

4.5.3 Adjustments for Exposure Duration

The IDA toxicity estimates are designated for specific exposure durations. All ECt_{50} values for inhalation exposures (and presumably also for ocular exposures) are reported to be for 2-min exposures for a minute volume of 15 liters (minute volume not relevant for ocular exposures).

In this analysis, the inhalation vapor toxicity low-percentile population estimates derived by the previously described methods are extrapolated for exposure durations of 10 min, 60 min, 8 hr, and 24 hr by using the time-scaling method (i.e., the ten-Berge model of $C^n \times t = K$, (see Appendix E); (ten-Berge, et. al., 1986) used in the derivation of the CWA AEGLs (NRC/COT, 2003).

4.5.3.1 Sulfur Mustard

In deriving an acute vapor AEGL 1 for HD, the NRC/COT (2003) used an n of 1 and 3 for time-scaling applications. The n of 1 was selected because HD is a direct contact poison and the AEGL 1 and AEGL 2 were based on direct ocular effects (i.e., for AEGL 1, conjunctival injection and minor discomfort with no functional decrement in human volunteers; for AEGL 2,

well-marked, generalized conjunctivitis, edema, photophobia, and eye irritation). An *n* value of 3 was used for deriving the 10-min and 30-min AEGL 3 values because the original data on which the AEGL 3 derivations were based were for exposure durations in mice greater than 30 min; and using an *n* of 3 provided the most protective values. The IDA inhalation vapor toxicity estimates for HD are for 2-min exposures; therefore, in this analysis, extrapolations to 10 min, 60 min, 8 hr, and 24 hr, follow the NRC/COT protocol for extrapolation for lower to greater time durations and are derived using the *n* value of 1.

4.5.3.2 Nerve Agents

In deriving acute vapor exposure guidelines for the nerve agents GA, GB, GD, GF, and VX, the NRC/COT (2003) used experimental data for agent GB (for time periods ranging from 10 min to 6 hr) to determine that the most appropriate *n* value to use for time scaling in the ten-Berge equation (for all effect levels) is 2. The *n* value of 2 was used to derive AEGLs for the time periods of 10 min, 30 min, 1 hr, 4 hr, and 8 hr. This same *n* value of 2 is used in the extrapolation of the low-percentile population IDA-based inhalation toxicity estimates to derive 10-min, 60-min, and 8-hr estimates. Because the maximum experimental exposure duration on which an *n* of 2 is based is 6 hr (see NRC/COT, 2003), the validity of using this same *n* of 2 for 24-hr estimates is uncertain. The NRC/COT would not normally apply the same *n* value for exposure durations 4 times longer than the experimental values. In such cases, the normal procedure recommended by the NRC/COT is to use the default *n* of 1 to go to longer exposure durations. This provides a more conservative (i.e., lower) final value. For these reasons, the 24-hr-inhalation-vapor-concentration estimates are derived in this report from the 8-hr estimates and using an *n* of 1, which is equivalent to a straight-line extrapolation. Therefore, the 24-hr-vapor-concentration estimates are one-third of the 8-hr estimates.

4.6 RESULTS

4.6.1 Inhalation and Ocular Vapor Criteria and Extrapolations

4.6.1.1 Estimated ECt_{01} and ECt_{16} Values for 2-Minute Exposures to Male Military Personnel

To demonstrate a range of hazard severity levels, the median inhalation/ocular toxicity values listed in the IDA report were used as the basis for extrapolating the 50^{th} percentile estimate to toxicity values corresponding to the 1^{st}, 16^{th}, 84^{th} and 99^{th} percentiles (see Appendix E, Table E-4). Specific focus was given to identifying a low-level negligible effect range. This analysis included a review of the probit-derived ECt_{01} and ECt_{16} estimates from the IDA ECt_{50} values for mild effects and, in keeping with IDA guidance to consider alternate, non-probit based methods and procedures, estimates were also derived from the three alternative methods described in Section 4.4 (see Table 4-2 for comparison of various estimate values). These estimates were further adjusted by time-extrapolation methods and susceptibility adjustment factors as needed.

Table 4-2. Comparison of Toxicity Estimates for Inhalation and Ocular Effects for Low Percentiles of the Male Military Population (units in mg-min/m^3)

Agent	IDA ECt_{50} (mild)[a]	Probit extrapolations[b]		ECt_{01} (mild) Approximation		
		ECt_{16} (mild)	ECt_{01} (mild)	Derived from ECt_{50} (severe): ECt_{50} (mild) Ratio[c]	Derived by Uncertainty Factor [d]	Derived by Lethality Ratio [e]
GA	1	**0.63**	**0.34**	0.02	0.1	0.33
GB	1	**0.63**	**0.34**	0.04	0.1	0.33
GD	0.4	**0.273**	**0.164**	0.006	0.04	0.13
GF	0.4	**0.253**	**0.137**	0.006	0.04	0.13
VX	0.1	**0.06**	**0.03**	0.001	0.01	0.03
HD	25	**11.7**	**4.2**	6.25	2.5	8.33

[a] From Grotte and Yang, 2001; values for male military personnel only, 2-min durations.

[b] Based on IDA ECt_{50} (mild) values probit; compound- and endpoint-specific but statistical reliability of ECt_{01} low.

[c] Based on ratio of severe and mild effect ECt_{50} values (see Appendix E, Table E-3); compound- and endpoint-specific, and function of probit; but severe and threshold probit slopes are dissimilar, making comparison less justifiable.

[d] Based on ECt_{50} (mild) values; UF =10 adjustment, as applied in RfD lowest-observed adverse effect level (LOAEL) to no-observed adverse effect level (NOAEL) extrapolation; non-standard method, no precedent.

[e] Based on ECt_{50} (mild) values divided by a lethality ratio factor of 3; presented only for comparative purposes; non-standard method, no precedent.

The log-probit ECt_{16} values for mild effects are considered relatively reliable upper-bound estimates of a negligibly severe population-effect range. For estimating the lower bound of such a range, the four methods represented in Table 4-2 demonstrate close similarity (less than an order of magnitude difference) between three of the methods, while one method (the severe-to-mild ratio approach) resulted in "outlier" estimates that were in the range of two orders of magnitude different from the others. Even though the severe-to-mild ratio approach is somewhat compound and endpoint-specific, it is noted that the probit-slope values for mild and severe ECt_{50} estimates are different, which makes this approach less desirable. As a preferred approach should be both compound and agent specific, the probit-derived ECt_{01} estimates for mild effects were selected as the best estimates for the lower bound (male military) population-effect level, though the uncertain statistical reliability of this 1st percentile estimate is acknowledged. It is noted that these estimates are still provided in milligram-minute per cubic meter (mg-min/m^3) and, therefore, do not address time-extrapolation factors. In addition, though these are reasonable low-end estimates for a male military population, they do not necessarily accommodate potentially more susceptible subpopulations, as has been described for inhalation and ocular pathways (Sections 4.2.1 and 4.2.2). These issues are addressed further in the following paragraphs.

4.6.1.2 Adjustments for Different Exposure Times

As noted in Section 4.5.3, estimates of inhalation vapor toxicity values for exposure durations of 10 min, 60 min, 8 hr and 24 hr have been derived using the ten-Berge equation—

$$\mathbf{C^n\ t = k}$$

4.6.1.3 Sulfur Mustard

The *k* value in the ten-Berge equation used to derive the HD concentrations for different time periods is based on the IDA-derived ECt_{01} or ECt_{16} mild values (see Table 4.2) and an *n* value of 1 (see Section 4.5.3)—

$$\mathbf{C^1\ t = k}$$

The IDA-derived ECt_{01} (mild) value for HD is 4.2 mg-min/m^3 for a 2-min exposure duration, or 2.1 mg/m^3 for 2 min. Therefore, *k* can be calculated as—

$$(2.1\ mg/m^3)^1 \times 2/60\ hr = k$$

$$\mathbf{k = 0.0699\ mg\text{-}hr/m^3}$$

Therefore, the HD concentration, EC_{01} (mild), in mg/m^3, for any exposure duration *t* (in hours) is—

$$\mathbf{EC_{01} = 0.0699/t}$$

For an 8-hr exposure period—

$$C = 0.0699\ mg\text{-}hr/m^3/8\ hr = 0.00875\ mg/m^3$$

4.6.1.4 Nerve Agents

The *k* value in the ten-Berge equation used to derive the nerve agent concentrations for exposure durations of 10 min to 8 hr is based on the IDA-derived ECt_{01} or ECt_{16} values for mild effects and an *n* value of 2 (see Section 4.5.3).

$$\mathbf{C^2\ t = k}$$

For agent GB, the IDA-derived ECt_{01} (mild) value is 0.34 mg-min/m^3 for a 2-min exposure duration (Table 4.2), or a concentration of 0.171 mg/m^3 for 2 min. Therefore, using an *n* of 2, the *k* value can be derived as—

$$(0.171 \text{ mg/m}^3)^2 \times 2/60 \text{ hr} = k$$

$$\mathbf{k = 0.000978 \text{ mg-hr/m}^3}$$

Therefore, the GB concentration, EC_{01} for mild effects (in mg/m^3), for any exposure duration *t* between 10 min and 8 hr (expressed in hours) would be—

$$EC_{01} = \sqrt{\frac{0.000978}{t}}$$

Therefore, the EC_{01} for mild effects for an 8-hr exposure to agent GB is—

$$C^2 = 0.000978 \text{ mg-hr/m}^3/8 \text{ hr}$$

$$C = 0.011 \text{ mg/m}^3$$

As discussed in Section 4.5.3, the 24-hr estimates for the nerve agents are based on straight-line extrapolations from the 8 hr values (i.e., $n = 1$).

The EC_{01}, EC_{16}, EC_{50}, EC_{84}, and EC_{99} values for mild effects for exposure durations of 10 min, 60 min, are presented in Appendix E, Table E-5; those for 8 hr and 24 hr are presented in Appendix E, Table E-6. The *k* values used to derive the 10-min, 60-min and 8-hr concentrations for the nerve agents, and the 10-min to 24-hr concentrations for HD from the ten-Berge equation are given in Appendix E, Table E-7.

***NOTE**: To obtain a concentration for a population percentile and exposure duration not covered in this report, a specific *k* for that population percentile must be derived from the original IDA data by first using the probit methodology described in Section 4.5.1 and Appendix E to obtain the *Ct* value for that particular percentile. The *Ct* is then converted to a 2-min *C* value, and then applied to the ten-Berge equation with the appropriate *n* value, as described above, to obtain the specific *k*.

The EC_{01} and EC_{16} values for mild effects from inhalation/ocular exposures for the male military population for the nerve agents and HD for the four time periods, 10 min, 60 min, 8 hr and 24 hr are presented in Table 4-3.

Table 4-3. Low-Percentile Male Military Population Effect Concentration (mg/m^3) Levels for Mild Inhalation/Ocular Vapor Exposures at Different Exposure Durations

	EC_{16} (mild effects) [a] (mg/m^3)				EC_{01} (mild effects) [b] (mg/m^3)			
	10 min	**60 min**	**8 hr**	**24 hr[c]**	**10-min**	**60-min**	**8 hr**	**24 hr[c]**
GA	0.141	0.058	0.020	0.0067	0.077	0.031	0.011	0.0037
GB	0.141	0.058	0.020	0.0067	0.077	0.031	0.011	0.0037
GD	0.06	0.025	0.009	0.003	0.037	0.015	0.005	0.0017
GF	0.06	0.023	0.008	0.0027	0.031	0.013	0.0044	0.0015
VX	0.013	0.0051	0.0018	0.0006	0.006	0.002	0.0008	0.00027
HD	1.165	0.1942	0.0243	0.0081	0.419	0.07	0.0087	0.0029

[a] Derived from the log-probit estimated ECt_{16} and the documented protocol of NRC/COT (2001); see Table 4-2.

[b] Derived from the log-probit estimated ECt_{01} and the documented protocol of NRC/COT (2001) ; see Table 4-2.

[c] For the nerve agents, derived by straight-line extrapolation from the 8-hr values.

4.6.1.5 Adjustments for Heterogeneous Populations and Comparisons with AEGLs

As discussed in Section 4.5.2, PTEs for a heterogeneous population are derived for the nerve agents by applying a UF of 10 to account for susceptible populations. For HD, a UF of 3 to protect potentially sensitive populations is applied. The resulting PTEs for inhalation/ocular vapor exposures are presented in Table 4-4, together with the AEGLs (NRC/COT, 2003) and AEGL equivalents (for 24-hr exposures) for these agents.

Table 4-4. Comparison of Agent Inhalation/Ocular PTEs[a] with AEGL-1 Values[b] (units in mg/m^3)

	10-min Exposure		60-min Exposure		8-hr Exposure		24-hr Exposure	
Agent	**PTE[d]**	**AEGL-1**	**PTE[d]**	**AEGL-1**	**PTE[d]**	**AEGL-1**	**PTE[d]**	**AEGL-1 Equiv.[c]**
GA	0.0077	0.0069	0.003	0.0028	0.0011	0.001	0.0004	0.0003
GB	0.0077	0.0069	0.003	0.0028	0.0011	0.001	0.0004	0.0003
GD	0.0037	0.0035	0.0015	0.0014	0.0005	0.0005	0.0002	0.0002
GF	0.0031	0.0035	0.0013	0.0014	0.0004	0.0005	0.0002	0.0002
VX	0.0006	0.00057	0.00017	0.00017	0.00008	0.000071	0.00003	0.000024
HD	0.14	0.41	0.023	0.067	0.0029	0.008	0.00097	0.003[d]

[a] Derived by dividing the EC_{01} estimates from the ten Berg equation by a UF of 10 for nerve agents and a UF of 3 for HD.

[b] AEGLs (NRC/COT, 2003).

[c] The AEGL protocol (NRC/COT 2001) does not advise extrapolation for exposure durations > 8 hr. These 24-hr "AEGL 1 equivalents" have no precedent and have been derived by straight-line extrapolation from the 8-hr AEGLs for use in this report only for purposes of comparison.

[d] NOTE: the "24-hour equivalent AEGL 1" estimate for the vesicant agent HD has been extrapolated from experimental, short-term human exposures of ≤33 min (Anderson, 1942). There are no human or animal experimental data from which to directly derive a long-term estimate for exposure durations approaching 24 hours. Extrapolation from short-term (≤33 min) data to 24-hr exposure duration is inherently uncertain. For an alkylating cell poison such as HD, there is always concern that extended exposures will result in cumulative effects. Available toxicological literature on the critical AEGL 1 effect (ocular: conjunctival injection and minor discomfort with no functional decrement, reversible: NRC/COT, 2003) indicates that no other organ system (e.g., respiratory tract, skin) would be adversely affected by exposure durations to the "24-hr equivalent" concentrations at durations > 8 hours, nor would potential additional ocular effects be permanent or disabling.

The original IDA-toxicity estimates were for 2-min exposures, and the IDA report specifically states "the accuracy of extrapolations beyond 60 min is unknown." However, in view of the close agreement between the 8-hr and 24-hr PTEs with the 8-hr AEGL 1 values and 24-hr AEGL 1 equivalents (especially for the nerve agents), the extrapolations from the IDA-toxicity estimates appear to be a reasonable approach to deriving PTEs. For HD, the estimated PTEs are in close agreement with the AEGL 1 estimates, from which they differ by an approximate factor of 3 (and are, therefore, more protective).

The EC_{16} values for mild effects, considered as upper bounds of the negligible severity range, are statistically derived concentrations at which 16 percent of an exposed population may experience mild effects as defined in the IDA report (for nerve agents, as a "level of symptom (e.g., ocular, rhinorrhea, and/or chest tightness) that might be noticed in the field"). Such effects are not life threatening, are fully reversible, and will not require medical treatment. These upper bounds of the negligible severity range can be compared to other toxicity values, such as the AEGL 2 estimates (NCR/COT, 2003). The EC_{16} values are well within an order of magnitude of the AEGL 2 estimates for 10 min, 60 min, and 8 hr, and the AEGL 2 equivalency estimates for 24 hr (see Table 4-5). AEGL 2 values for nerve agents are derived from human exposure studies in

which the principal observed effects are consistent with the EC_{16} (mild) definition in the IDA report. Therefore, the principal-operational effect common to both the IDA-derived EC_{16} values and the AEGL 2 values are reversible ocular effects, but which, under certain circumstances (i.e., low ambient light), might result in reduced visual acuity. Table 4-5 demonstrates this comparison.

Table 4-5. Comparison of Agent Inhalation/Ocular EC_{16}[a] (mild) Values with AEGL-2 Estimates[b] (units in mg/m^3)

	10-min Exposure		60-min Exposure		8-hr Exposure		24-hr Exposure	
Agent	**EC_{16}**	**AEGL 2**	**EC_{16}**	**AEGL 2**	**EC_{16}**	**AEGL 2**	**EC_{16}**	**AEGL 2 Equiv.[c]**
GA	0.141	0.087	0.058	0.035	0.020	0.013	0.012	0.0043
GB	0.141	0.087	0.058	0.035	0.020	0.013	0.012	0.0043
GD	0.06	0.044	0.025	0.018	0.009	0.0065	0.005	0.0022
GF	0.06	0.044	0.023	0.018	0.008	0.0065	0.005	0.0022
VX	0.013	0.0072	0.0051	0.0029	0.0018	0.0010	0.0011	0.00033
HD	1.165	0.60	0.1942	0.10	0.0243	0.013	0.0081	0.0042[d]

[a] Derived from the IDA 2-min Ct values.

[b] AEGLs (NRC/COT, 2003).

[c] The AEGL protocol (NRC/COT, 2001) does not include extrapolation for exposure durations >8 hr; these 24-hr AEGL-2 equivalents have been derived in this report by straight-line extrapolation from the 8-hr values for purposes of comparison.

[d] NOTE: the "24-hour equivalent AEGL 2" estimate for the vesicant agent HD has been extrapolated from experimental, short-term human exposures (Anderson, 1942). There are no human or animal experimental data from which to directly derive a long-term estimate for exposure durations approaching 24 hours. Extrapolation from short-term data to 24-hr exposure duration is inherently uncertain. For an alkylating cell poison such as HD, there is always concern that extended exposures will result in cumulative effects. Available toxicological literature indicates that the critical AEGL 2 effects are on the eyes (i.e., generalized conjunctivitis, edema, photophobia and eye irritation). These effects are non-life threatening but may result in effective performance decrement and therefore be categorized as a military casualty (NRC/COT, 2003).

***NOTE:** A comparison of the AEGL 3 levels with the various IDA-derived toxicity values was performed, and it was noted that the AEGL 3 levels for all the agents were less than the LC_{01} estimates derived from IDA. In fact, for nerve agents, the AEGL 3 values were below the EC_{01} (severe) estimates (though above the EC_{99} (mild)). For HD, the AEGL 3 was between the EC_{01} (severe) and the EC_{16} (severe) estimates.

4.6.1.6 Conclusions and Recommendations for Determining Hazard Severity Ranges for Inhalation/Ocular Vapor Exposures

The IDA inhalation/ocular vapor toxicity estimates, in conjunction with directly applied probit slopes, can provide a reasonable range of toxicity estimates for most military applications. The EC_{16} values derived from the IDA report have reasonable statistical reliability as they represent one standard deviation from the mean. They can be considered the upper bounds of the negligible hazard severity effect range. Best estimates of the lower bound of the negligible hazard severity effect range can be derived from the compound and endpoint-specific probit

calculated ECt_{01} values with added agent-specific adjustment factors for susceptibility applied for a heterogeneous population. These lower bounds represent reasonable PTEs.

For time extrapolations, the ten-Berge model ($C^n \times t = k$), can be used to derive concentrations between 10 min and 24 hr, where $n = 2$ for nerve agent exposures of 10 min to 8 hr, and straight-line extrapolation from the 8-hr value is used to derive concentrations between 8 hr and 24 hr; and $n = 1$ for HD for exposure durations of 10 min to 24 hr, by using the k values derived from the IDA values, as presented in Appendix E, Table E-7.

The PTEs derived for heterogeneous populations from the probit analysis when compared to the AEGL 1 values suggests that the use of PTE values as a lower bound is reasonable and consistent with established toxicity values for the general public (NRC/COT, 2003).

Therefore, it is recommended that the EC_{16} values for mild effects be used as the upper bound of the negligible severity range and that the EC_{01} values for mild effects, adjusted for a heterogeneous population with the use of the appropriate UF, be used as the lower bound of this negligible severity range (Table 4-6).

Table 4-6. Recommended Range of Negligible Severity (Low-Level) Effect Concentrations (mg/m^3) for Inhalation/Ocular Vapor Exposures of Different Exposure Durations

	Upper Bound of Range: EC_{16} (mild effects) [a] mg/m^3				Lower Bound of Range: PTE [b] mg/m^3			
	10-min	**60-min**	**8 hr**	**24 hr[c]**	**10-min**	**60-min**	**8 hr**	**24 hr[c]**
GA	0.141	0.058	0.020	0.0067	0.0077	0.003	0.0011	0.0004
GB	0.141	0.058	0.020	0.0067	0.0077	0.003	0.0011	0.0004
GD	0.06	0.025	0.009	0.003	0.0037	0.0015	0.0005	0.0002
GF	0.06	0.023	0.008	0.0027	0.0031	0.0013	0.0004	0.0002
VX	0.013	0.0051	0.0018	0.0006	0.0006	0.00017	0.00008	0.00003
HD	1.165	0.1942	0.0243	0.0081	0.14	0.023	0.0029	0.00097

[a] Derived from the IDA 2-min Ct values.
[b] EC_{01} values derived from IDA 2-min Ct values, adjusted for heterogeneous population with a UF of 10 for the nerve agents and a UF of 3 for HD.
[c] 24-hr values for the nerve agents derived by straight-line extrapolation from the 8-hr values.

4.6.2 Percutaneous Vapor Criteria and Extrapolations

The IDA toxicity estimates and probit slopes for percutaneous vapor exposures (see Appendix B) to military personnel are for unclothed persons (70-kg males). For nerve agents, it is assumed that soldiers are masked and possess full eye protection. The IDA report does not discuss body region variation in skin absorption and susceptibility to the agents; it is, therefore, not totally clear if toxicity values for "threshold" effects are sufficiently protective for sensitive body

regions, such as the groin and scrotum. However, because the IDA values are reported to be for unclothed persons (and assuming that unclothed meant complete nudity), it is inferred that the IDA estimates would incorporate exposure to the most susceptible body regions; therefore, the assumption is made here that the IDA values are protective for the most susceptible body regions. The IDA report defines percutaneous vapor "threshold" for nerve agents as "a slight ChE inhibition," and is, therefore, a systemic-effect endpoint. Threshold effects for HD are defined as "the midpoint of the dosage range at which effects begin to occur in the sample population;" however, the types of effects are not described.

4.6.2.1 Estimated ECt_{01} and ECt_{16} Values for Percutaneous Vapor Exposures

To demonstrate a range of hazard severity levels associated with percutaneous vapor exposures, the median percutaneous vapor toxicity values listed in the IDA report were used for extrapolating the 50^{th} percentile estimate to toxicity values corresponding to the 1^{st}, 16^{th}, 84^{th}, and 99^{th} percentiles (see Appendix E, Table E-8). As noted earlier, extrapolations below 16 percent and above 84 percent are not considered highly reliable due to large uncertainties in the confidence limits of such estimates. However, specific focus was given to identifying a low-level, negligible effect range that included a review of the probit-derived ECt_{01} and ECt_{16} estimates from the IDA report. In keeping with IDA guidance to consider alternate, non-probit based methods and procedures, estimates were also derived from the three alternative methods described in Section 4.5.1. The results are presented in Table 4-7. As with the inhalation/ocular vapor toxicity estimates, the log-probit ECt_{16} values can be viewed as relatively reliable upper-bound estimates of a low-percentile healthy male military population effect level. For the lower-bound estimate, it is interesting to note that the ECt_{01} (threshold) estimates for percutaneous vapor derived from all four methods are within the same order of magnitude. This provides added confidence to the overall analysis. For percutaneous vapor exposures, ECt_{01}(threshold) estimates derived from the ratios of the ECt_{50} values for threshold and severe effects are consistent with the logic of the IDA report in that they are agent-specific and have comparable probit slopes (unlike the case with inhalation/ocular vapor toxicity estimates for which the probit slopes are different). Therefore, at this time, these ratio-derived values are selected as the best estimate of the lower bound of the negligible hazard severity range of percutaneous vapor estimates. This same conclusion was reached by Watson, et. al., (2003) in an analysis of exposure guidelines for use in developing chemical protective ensembles for civilian emergency responders.

Table 4-7. Comparison of Toxicity Estimates for Percutaneous Vapor Effects for Low Percentiles of the Male Military Population (units in mg-min/m^3)

Agent	ECt_{50} (threshold)[a] mg-min/m^3	Probit Extrapolations[b]		ECt_{01} (threshold) Approximation		
		ECt_{16} (threshold)	ECt_{01} (threshold)	Derived from Ratio of Threshold: Severe Effect [c]	Derived by Uncertainty Factor [d]	Derived by Lethality Ratio [e]
GA	2000	**1265**	685	**333**	200	667
GB	1200	**759**	411	**180**	120	400
GD	300	**205**	123	**45**	30	100
GF	300	**190**	103	**45**	30	100
VX	10	**6.8**	4.1	**4**	1	3.3
HD	25	**11.7**	4.1	**3**	2.5	8.3

Bolded values are the recommended upper and lower limits for application to deployed personnel using established military ORM doctrine. For civilian populations/other applications, risk-acceptance levels and associated upper bound of toxicity ranges may be lower (for example, see Watson, et al., 2003).

[a] From Grotte and Yang 2001; values for male military personnel only.

[b] Compound- and endpoint-specific, however, statistical reliability of ECt_{01} is low.

[c] Compound- and endpoint-specific; dependant on similarities in the probit slopes.

[d] Based on ECt_{50} (threshold) values; UF =10 adjustment as applied in RfD LOAEL to NOAEL extrapolation.

[e] Based on ECt_{50} (threshold values) divided by a factor of 3; presented only for comparative purposes.

4.6.2.2 Adjustments for Different Exposure Times

The IDA report describes all ECt_{50} values for percutaneous vapor exposures to be for 30-min exposures and states that the accuracy of extrapolations of the toxicity estimates to exposure times beyond 2 hours is unknown. No guidelines are provided for extrapolating the percutaneous vapor toxicity estimates from 30 min to other exposure durations of less than 30 min or from 30 min to 2 hr. It appears that the state of modeling tools and data currently available for percutaneous vapor toxicity estimation cannot discriminate between concentrations of concern for exposure durations between 30-50 min. Therefore, for a given endpoint and scenario, it may be reasonable and would be protective to assume that the *Ct* estimates should be constant for exposure durations between 30 min to 2 hr.

4.6.2.3 Adjustments for a Heterogeneous Population

As previously discussed, susceptibility for percutaneous exposures is primarily a factor of body region variation. Intraspecies variation is considered less significant; therefore, a UF of 1 is used for adjustment to a heterogeneous population.

4.6.2.4 Conclusions and Recommendations for Determining Hazard Severity Ranges for Percutaneous Vapor Exposures

The IDA percutaneous vapor toxicity estimates, in conjunction with directly applied probit slopes, can provide a reasonable range of toxicity estimates for most military applications. The ECt_{16} (threshold) values derived from the IDA ECt_{50} (threshold) values are considered protective for the more susceptible body regions and have reasonable statistical reliability; therefore, they can be considered upper-bound estimates of a low-level exposure negligible-severity range. Lower-bound estimates are derived using compound- and endpoint-specific data. An ECt_{01} (threshold) estimate determined directly from probit extrapolation was considered. However, given the statistical unreliability and in an attempt to provide a protective estimate, the preferred estimate was derived by applying a chemical-specific-effects ratio (severe to threshold) to the ECt_{50} (threshold). As susceptibility is a factor of body region variation more so than intraspecies variation, these estimates are also considered applicable to a heterogeneous (mixed) population and, therefore, represent the PTE. Table 4-8 presents the recommended range of low-level toxicity estimates that bound the negligible severity range.

For time extrapolations, it is considered reasonably protective to assume that the *Ct* estimates would be constant for exposure durations between 30 min and 2 hours.

Table 4-8. Recommended Range of Negligible Severity (Low-Level) Effect Concentrations (mg/m^3) for Percutaneous Vapor Exposures of Different Exposure Durations

	Upper Bound of Range: EC_{16} (threshold effects) [a] (mg/m^3) [c]			Lower Bound of Range: PTE [b] (mg/m^3) [c]		
	30 min	**60 min**	**2 hr**	**30 min**	**60 min**	**2 hr**
GA	42.17	21.08	10.54	11.1	5.55	2.77
GB	25.3	12.65	6.33	6	3	1.5
GD	6.83	3.42	1.71	1.5	0.75	0.375
GF	6.33	3.17	1.58	1.5	0.75	0.375
VX	0.223	0.113	0.057	0.133	0.067	0.033
HD	0.39	0.195	0.975	0.1	0.05	0.025

[a] Derived from the ECt_{16} values.
[b] EC_{01} values derived from IDA 2-min Ct values, adjusted for heterogeneous population with a UF of 10 for the nerve agents and a UF of 3 for HD.
[c] NOTE: The corresponding Ct values can be derived by multiplying the listed concentrations by the exposure duration in minutes.

4.6.3 Percutaneous Liquid Criteria and Extrapolations

The toxicity estimates presented in the IDA report for percutaneous exposures to agent liquid are for only two endpoints - lethality (LD_{50}) and severe effects (ED_{50}) (see Appendix B).

4.6.3.1 Estimated EDt_{01} and EDt_{16} Percutaneous Liquid Values for Male Military Personnel

Estimation of effects resulting from percutaneous liquid exposure is one of the least characterized areas examined in the current analysis. Available estimates are highly derivative (NRC/COT, 1997; Grotte and Yang, 2001), and, therefore, more susceptible to extrapolation error. This is particularly true for the case of HD.

As noted above, the IDA-toxicity estimates are for only two endpoints: lethality (LD_{50}) and severe effects (ED_{50} (severe)). The median toxicity values for severe and lethal effects were used to extrapolate, by probit analysis, to toxicity values corresponding to the 1st, 16th, 84th, and 99th percentiles of the population. These values are presented in Appendix E, Table E-9.

Though no military estimates have been derived for threshold or mild effects to liquid exposure, this analysis considers the application of the several methods to derive estimates of "threshold" or mild effects from the ED_{50} values for severe effects. These approaches are described below, and the results summarized in Table 4-9.

One approach to estimate ED_{50} values for threshold effects for liquid exposures is by applying the chemical-specific ratios of the IDA ECt_{50} (threshold) and ECt_{50} (severe) percutaneous vapor estimates to the percutaneous liquid ED_{50} (severe) estimates. For example, for percutaneous vapor exposures to agent GA, the ECt_{50} (threshold) is 2000 mg/m^3 and the ECt_{50} (severe) is 12000 mg/m^3; resulting in a ratio of 1:6 or 0.167. Assuming that the same ratio would apply to liquid exposures, this value is multiplied by the ED_{50} (severe) for liquid exposures (900 mg) to derive the threshold ED_{50}—

$$ED_{50}\ (threshold) = 900\ mg \times 0.167 = 150\ mg$$

Probit analysis can then be used to derive the ED_{16} and ED_{01} (threshold) values. These values are shown in Table 4.9. As previously indicated, the ED_{16} values are considered statistically robust and provide a reasonable upper bound to the negligible severity range. However, because the ED_{16} values are not derived directly from a threshold value but are highly derivative, a high level of confidence cannot be assigned to the values.

The ED_{01} (threshold) values can also be estimated using two of the approaches described in Section 4.5.1. In one case, the ED_{01} values are estimated by applying a UF of 10 to the derived ED_{50} (threshold) values (equivalent to procedure for estimating NOAELs from LOAELs). In the second case, the ED_{01} values are estimated using the lethality ratio which, as discussed in Section 4.5.3, is approximated by a factor of 3.

The three methods provide estimates of ED_{01} (threshold) values that differ by only a factor of about 3 (see Table 4-9). For most agents, these values appear to be in reasonable agreement with the available experimental toxicity data. For example, Grob, et .al., (1953) reported that 20 mg of GB dissolved in propylene glycol and applied to the forearm caused no signs or symptoms of

toxicity but did result in a 22 percent reduction in RBC-ChE activity, and Freeman, et. al., (1954) reported that a GA dose of about 400 mg applied to the skin caused no clinical signs of toxicity. For HD, the critical exposure factor is the maximum amount of agent at a particular site on the skin; therefore, the values given in Table 4-9 must be converted to milligrams of agent per unit body surface area. The HD ED_{16} of 28 mg converts to an exposure of 1.5 microgram per square centimeter ($\mu g/cm^2$) (assuming 1.8 square meter (m^2) body surface area). In comparison, Landahl (1945) reported that in tests on human volunteers, a dose of 2.5 µg resulted in erythema in 87 of 209 individuals and blistering in 5 test subjects.

In the case of VX, there is experimental data showing that a dose as low as 5microgram per kilometer (µg/kg) (equivalent to 0.35 mg for a 70-kg man), when applied to the head, cheek, or earlobes, caused moderate signs of toxicity in 11 of 24 individuals and minor symptoms in 4 of 24 individuals (Sim, 1962). In another study, however, a similar amount of VX, when applied to the forearm, was estimated to cause only mild effects in 1 percent of the test population (DA, 1974). These results suggest significant body region differences in VX absorption. Because of concerns for VX, the lowest-derived ED_{01} (threshold) values shown in Table 4-9 are preferred lower-bound estimates of the negligible severity range. These values were derived by applying a UF of 10 to the ED_{50} (threshold) values. It is acknowledged that these estimates may be overly conservative for some of the agents, but they would include an adequately protective lower bound for VX.

Table 4-9. Derived Percutaneous Liquid Threshold Effect Toxicity Estimates for Low Percentiles of the Male Military Population (in mg/70-kg person)

Agent	Derived ED_{50} (threshold) [a]	Probit Application to Derived ED_{50} (threshold)		Approximated ED_{01} (threshold)	
		Approximated ED_{16} (threshold)	Approximated ED_{01} (threshold)	From derived ED_{50} (threshold) with application of UF of 10[b]	From derived ED_{50} (threshold) with application of Lethality Ratio[c]
GA	150	**95**	51	**15**	50
GB	150	**95**	51	**15**	50
GD	30	**20**	12	**3**	10
GF	30	**19**	10	**3**	10
VX	0.8	**0.55**	0.33	**0.08**	0.27
HD	60	**28**	10	**6**	20
Bolded values are the recommended upper and lower limits for application to deployed personnel using Established military ORM doctrine.					

[a] Based on chemical-specific ratio of percutaneous vapor ECt_{50} *(threshold)* to ECt_{50} *(severe)* values from the IDA report (Grotte and Yang, 2001).

[b] Derived from estimated ED_{50} (threshold) with application of UF of 10.

[c] Derived from estimated ED_{50} (threshold) with application of "lethality ratio" of 3.

4.6.3.2 Adjustments for Different Exposure Times

The percutaneous liquid toxicity estimates proposed in the IDA report are for a single total dose (in mg) for an unclothed 70-kg man. Although not specifically stated in the IDA report, the assumptions are made here that the estimates represent total applied dose (not absorbed dose), and that they are for an indefinite duration of skin contact exposure. Consequently, no adjustments have been considered necessary for exposure duration.

4.6.3.3 Adjustments for Heterogeneous Populations

As previously discussed, susceptibility for percutaneous exposures is primarily a factor of body region variation. Intraspecies variation is considered less significant and, therefore, a UF of 1 is used for adjustment to a heterogeneous population.

4.6.3.4 Conclusions and Recommendations for Determining Hazard Severity Ranges for Percutaneous Liquid Exposures

Estimation of effects resulting from percutaneous liquid exposure is one of the least characterized areas examined in the current analysis. The IDA percutaneous liquid toxicity

estimates and applied probit slopes can only provide a limited range of toxicity estimates reflecting significantly adverse health effects. However, the available data can be used to derive an estimated range of negligible severity toxicity estimates including a derived ED_{16} (threshold) estimate (upper bound of negligible severity range) and an approximated ED_{01} (threshold). The most reasonable approach for deriving these threshold-effect levels for percutaneous liquid exposures considers chemical- and effect-specific factors and the agent-specific, dose-response curve as defined by the probit slope. However, because there are no IDA-median (50^{th} percentile) toxicity values for threshold/mild effect to percutaneous liquid exposures, an additional layer of extrapolation is needed. This results in lower confidence in the derived low-level estimates. However, comparisons with experimental data suggest that the recommended range of low-level toxicity estimates presented in Table 4-10 provide a reasonable characterization of the negligible severity range for percutaneous liquid exposures. As susceptibility to percutaneous exposure is a factor of body region variation more so than intraspecies variation, it is noted that the values can be applied to a heterogeneous population; therefore, the lower-bound estimate reflects a PTE. The percutaneous exposure PTE is particularly appropriate for assessing effects to susceptible body regions such as head, neck, and groin.

Table 4-10. Recommended Range of Negligible Severity (Low-Level) Effect Levels for Percutaneous Liquid Exposures

Agent	Upper Bound of Range: ~ED_{16} (threshold)		Lower Bound of Range: PTE	
	Units = mg/70-kg person	Units = [a] µg/cm^2	Units = mg/70-kg person	Units = [a] µg/cm^2
GA	95	5.28	15	0.83
GB	95	5.28	15	0.83
GD	20	1.1	3	0.167
GF	19	1.06	3	0.167
VX	0.55	0.03	0.08	0.004
HD (hot temp.)	28	1.5	6	0.3

[a] Estimates also provided in µg/cm^2 of skin surface area - determined by assuming 1.8 m^2 total body surface area of average male (NRC/COT, 1997).
(For civilian populations/other applications, risk-acceptance levels and associated upper and lower bounds may vary). (See Watson, et al. 2003.).

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SECTION 5
CONCLUSIONS AND RECOMMENDATIONS: OPERATIONAL RISK MANAGEMENT OBJECTIVES AND ASSOCIATED TOXICITY ESTIMATES

5.1 GENERAL

Historically, the military risk assessment and decision making regarding CWA exposures has been based on a "go/no-go" single risk-level concept. This approach is inconsistent with the ORM framework that is required in other aspects of military decision making and limits the flexibility that a commander has to balance overall risks and maximize overall safety and mission success. The recent DATSD-CBD endorsed interim toxicity estimates for GA, GB, GD, GF, VX and HD (Grotte and Yang, 2001), provides information that can now be used in military ORM applications.

With proper extrapolation to address exposure durations, and susceptible sub populations, these toxicity values can be used to describe the full range of military population health effects from these chemicals. This range is necessary to address desired objectives of critical chemical defense measures including Modeling and Simulation (Planning and Prediction), Contamination Avoidance, Protection, Decontamination, and Medical Interventions.

The toxicity estimates and extrapolation alone do not directly correspond with doctrinally defined levels of hazard severity or risk. Specific description of health effects (and some level of indirect resource impacts) caused by chemical exposures must be specifically assigned to the established ORM framework. The associated toxicity levels can then be tied to the ORM framework to assist in determining specific military chemical defense objectives.

5.1.1 DATSD-CBD Interim-Certified Military Toxicity Estimates

5.1.1.1 Uncertainties and Susceptible Subpopulations

Currently endorsed DATSD-CBD CWA acute interim-certified toxicity values presented in the IDA report provide median (50^{th} percentile) population estimates and probit values for "70-kg male soldiers." For many of the chemicals and endpoints, the uncertainty in the estimates is significant, including the added uncertainty of the potential increased susceptibilities within an increasingly diverse military force (e.g., gender, age, ethnicity, physiological status, and genetic traits). It is concluded that the deployed military population includes individuals with specific types of genetic and/or physiological susceptibilities to nerve agents and HD, very likely at percentages not substantially different from a heterogeneous civilian population (USACHPPM, 2003a). With the exception of readily identifying females (who appear to be more susceptible than males to effects of nerve agents (see Section 4.2.2), the identification and determination of percentages of all deployed persons with increased susceptibilities to these agents (and the degree of their increased susceptibility) cannot be definitively quantified at present. Reviews of deployment demographics over the last decade exhibit increasing diversity and greater

similarities to features of the adult civilian population (largely due to increasing use of National Guard and Reserve forces and deployment of civilian contractors). Thus, the variation and extent of susceptibilities in the heterogeneous general population are now more likely to be reflected in the present deployed force. For example, in current Operation Iraqi Freedom operations, over a quarter of deployed troops are over 35 years of age (just over 1 percent are over 50 years), and approximately 10-15 percent of deployed personnel are females. Another significant factor is ethnic diversity leading to the possible presence of some pre-disposing susceptibility factors based on genetics and age (see USACHPPM, 2003a, Appendix F for more details). Existing respiratory disease can be reasonably estimated in well over 5 percent (as high as 60 percent) (USACHPPM 2003a, Appendix F; Joint Staff Central Command (CENTCOM) TPS, February 2003; and CENTCOM JTPR, 2001-2003). Therefore, even without accounting for the portion of the male personnel who may also be more susceptible to the effects of these agents, it can be estimated that at least 10-15 percent of a military population may be genetically pre-disposed to exhibit nerve agent effects at lower levels than that of the average 70-kg healthy male military population represented by the interim-certified toxicity values. Considering the additional age, genetic, behavioral, and stress factors that can increase susceptibility, it is conceivable that, for certain chemical exposures, greater than 20 percent of the deployed force could be at greater risk of developing adverse health effects than the "average" healthy young deployed male. Data gaps regarding specific demographic and genetic profiles of deployed forces preclude more quantified estimates of the extent of impact.

5.1.1.2 Applications

Despite these uncertainties, the interim-military toxicity estimates and probit slopes are considered adequate for the purpose of gross identification and assessment of CWA hazards, particularly for determining general ORM hazard severity (i.e., Catastrophic, Critical, Marginal, Negligible). However, for specifically estimating the low-level to no-effect range, some additional adjustment to these estimates is necessary.

***NOTE:** These adjustments can accommodate FHP requirements but are not generally suitable for all Homeland Security applications due to additional civilian protective requirements.

The interim-certified lethal toxicity estimates are also adequate for establishing worst-case, maximum exposure criteria for testing protective measures and medical countermeasures. When used for quantitative casualty estimation, the uncertainties must be clearly understood and accepted. For determining the bounds of the four categories of hazard severity, existing ORM definitions of unit degradation and mission impact can be translated into types and approximate percentages of casualties, which include consideration of fatalities, incapacitating and non-incapacitating health effects, and general assumptions regarding associated indirect (non-casualty) resource losses. Table 5-1 presents general hazard severity definitions and associated ranges of toxicity estimates that represent each category.

5.1.1.3 Time Extrapolation

As described in the IDA report, the toxicity values for inhalation vapor exposures were intended for very brief exposure durations of 2 minutes. The IDA report further describes time extrapolation for inhalation and ocular exposures as based on Haber's Law (which is a linear extrapolation where multiplication of the concentration *C x time t* is a constant). However, the IDA report notes that this may not be the most accurate method for extrapolation. The availability of new data and subsequent peer-reviewed documents allows a more refined approach to time extrapolation, as described and documented in the current evaluation.

Table 5-1.
ORM Hazard Severity Definitions and Associated Toxicity Ranges for Chemical Exposures[a]

Hazard Severity	Health Impacts Associated with Hazard Severity Level[b]	Associated Toxicity Ranges
CATASTROPHIC	Increasing deaths and casualties with severe disabling/incapacitating effects requiring significant medical attention (e.g., Echelon IV) and/or additional personnel support for survival.	*Upper bound: unlimited* *Lower bound:* *> LCt_{16} and/or* *> ECt_{50} or ED_{50} (severe effects)* *(whichever lower)*
CRITICAL	Few, if any, deaths but significant numbers of disabling/incapacitating casualties, many requiring medical treatment or support (e.g., minimum Echelon III, possibly Echelon IV); others are likely to have noticeable but not disabling health effects.	*Upper bound:* *< lower bound Catastrophic)* *Lower bound:* *> ECt_{01} or ED_{01} (severe effects) and* *> ECt_{50} or ED_{50} (mild or threshold effects)* *(whichever lower)*
MARGINAL	Many persons may have noticeable but not disabling health effects; and/or the potential for individuals to have reversible, delayed (post-mission or deployment) health effects is considered very possible. The acute (observable) effects require minimal medical attention but may enhance stress-related casualties.	*Upper bound:* *< lower bound Critical* *Lower bound:* *> ECt_{16} or ED_{16} (mild or threshold effects)* ***(see footnote)[c]***
NEGLIGIBLE	Few if any persons expected to have noticeable health effects. The potential for individuals to have delayed (post-conflict) health concerns is considered minimal to none. Low-level exposures fall into this hazard severity category.	**"Low-level range"** *Upper bound:* *< lower bound Marginal; i.e.,* *≤ ECt_{16} (mild or threshold effects)* *Lower bound: theoretically extending to "0", the practical lower-bound is represented by a PTE which is the level below which no-health effects would be expected in any of exposed population, including susceptible sub-groups)* ***(see footnote)[c]***

[a] The Hazard category definitions here are generic and apply to any type of chemical hazard, including both chemical warfare and TICs.

[b] See Section 2 of this report as to how these hazard categories apply to the ORM process and how these definitions accommodate existing ORM risk definitions and established unit degradation criteria.

[c] It is noted that, based on assessment of current toxicity data, "Marginal" and "Negligible" exposures to nerve and vesicant agents are neither associated with delayed health effects, nor with long-lasting signs of any clinical significance.

5.1.2 Low-Level Toxicity Criteria (Negligibly Severe Effects Range)

Because many strategic decisions are based on the concept of "low-level" exposure estimates associated with minimal or no-health effects within an exposed population, this report has focused on defining best estimates of toxicity for the Negligible hazard severity range. These criteria are now necessary for FHP surveillance and documentation of potential exposures as required by Joint Staff policy (MCM, 2002a, and 2002b) that requires all chemical exposures (to CWA as well as TICs) be documented. Low-level toxicity criteria are also needed to strategically establish acceptable-risk level objectives for detection and protection specifications. As described in Section 2.4 of this report, low-level includes exposure levels (as a function of concentration and exposure time) that reflect negligibly severe hazards that will not adversely impact mission success. Specifically, low-level is not a single level but a range of exposure levels that reflect varying potential for mild acute, delayed, or no-adverse health effects in a small portion of an exposed population. The lower bound of the negligible range is intended to represent toxicity levels that represent a PTE below which health effects are not expected for those who are particularly susceptible to the effects of a chemical.

5.1.3 Exposure Pathway-Specific Issues

5.1.3.1 Inhalation/Ocular Vapor Exposures

Exposures through inhalation/ocular vapor routes are the most critical for assessing most scenarios. Such exposures are more difficult to avoid and affect the most sensitive target organs. Most existing detection devices are designed with detection limits provided as a concentration level (mg/m^3) (see Appendix D, Table D-1 for summary of existing equipment); therefore, the IDA-based toxicity estimates must be translated into duration-specific concentrations. Time extrapolation for nerve agents is not a simple linear equation and should reflect the recommended algorithm of $C^2t = k$ for exposure durations of 10 min to 8 hr. For nerve and HD estimates between 8 hours and 24 hours, a straight-line extrapolation from the 8-hr values is recommended.

Inhalation/ocular vapor exposure is also critical to civilian applications. Federally endorsed acute-inhalation toxicity-based criteria (known as AEGLs) as applied to civilian emergency planning and response efforts, have been published (NRC/COT, 2003). It is noted that toxicity values at the lower bound of the Negligible range (i.e., the PTEs derived from the IDA-toxicity estimates) are very similar to the AEGL 1 values. Likewise, the upper bound of the Negligible range, defined by the IDA-derived EC_{16} (mild) levels, are within the same order of magnitude as the AEGL 2 levels for CW agents. These similarities are particularly interesting given that different models (and some different data) were used to establish each set of values. This comparison provides added confidence in the protective nature of the PTE estimates and the appropriateness of the EC_{16} values as limits of the upper bound of the Negligible severity range. AEGL 3 values reflect significant severe effects levels but appear to lie below military LC_{01} estimates (and are, therefore, protective). As the IDA report specifically states that its toxicity estimates are not for civilian use, consideration of AEGLs is particularly important when addressing Homeland Security needs. Compared with Homeland Security objectives, some

military applications may require less stringent (protective) toxicity-based criteria for detection, protection, or decontamination. However, DOD should be prepared with a position as to the appropriate toxicity values for Homeland Security applications including those used in the specifications for detection and monitoring equipment and PPE. For those applications that are specifically for civilian scenarios, the AEGLs should be preferentially used because they are Federally endorsed for such applications. An example of this is provided by the CSEPP Policy Paper Number 20 (CSEPP, 2003) signed by both the Army and FEMA. This policy paper pertains to the CSEPP, which is designated for mitigation and advance planning for local impacts from potential accidents at the nation's CWA stockpile facilities. A number of CSEPP states are currently implementing the guidelines contained within the CSEPP (2003) policy paper.

5.1.3.2 Percutaneous Vapor Exposures

Single-route absorption of agents through skin from vapor exposures is a substantially less hazardous exposure route than that from vapor eye contact or inhalation in that much higher vapor concentrations are required to produce toxic effects via percutaneous exposures. So, for vapor detection criteria, the more protective inhalation/ocular-based toxicity estimates should be used.

5.1.3.3 Percutaneous Liquid Exposures

Exposure to percutaneous liquid agent is extremely hazardous but is also the most controlled and/or avoidable of the exposure routes. However, one area of concern is to assess potential for residual surface contamination, especially to verify decontamination. Estimation of effects resulting from percutaneous liquid exposure is one of the least characterized areas examined in the current analysis. The IDA percutaneous liquid toxicity estimates and applied probit slopes can, therefore, provide only a limited range of toxicity estimates reflecting significantly adverse health effects. However, the available data can be used to derive an estimated range of negligible severity toxicity estimates including a derived ED_{16} (threshold) estimate (upper bound of negligible severity range) and an approximated PTE. These are very low-confidence estimates but may be used in limited applications to address complex decontamination scenarios.

5.2 RECOMMENDATIONS

5.2.1 Translating Toxicity Information into the Operational Risk Framework

The December 2001 DATSD-CBD acute CWA interim-certified toxicity estimates and probit slopes provide a range of data that should be used to complement the existing military ORM framework. This will ensure consistency with existing risk management doctrine and will accommodate current FHP requirements. Specifically, the severity of the health effects reflected by the different toxicity estimates should be used to represent ORM hazard severity categories (i.e., Catastrophic, Critical, Marginal, Negligible) as demonstrated in Table 5-1.

5.2.2 Defining Low-Level Exposures

The USACHPPM recommends that the term "low-level exposures" should be doctrinally defined as exposures that represent a Negligible hazard severity (as defined in ORM terms in Table 5-1). This category is the most critical hazard severity to define, as substantial chemical defense applications (i.e., contamination avoidance (detection) and protection) require the application of toxicity values to ensure that Negligible hazard severity levels are achieved. Because the interim-military estimates are median values (statistically estimated to affect 50 percent of the exposed population) and are definitively described as applicable to "healthy 70-kg male soldiers" only, particular attention was given in this report to assess additional data and toxicity-based values that apply to the more diverse contemporary military population. Therefore, it is conceivable that 20 percent or even more of a military population may be genetically and physiologically pre-disposed to exhibit nerve agent effects at lower levels than that of the average "healthy male military" population currently represented by the interim-military toxicity estimates. It is concluded that, with appropriate extrapolation and adjustments to reflect data uncertainties and the potential for increased susceptibility, the DATSD-CBD interim-certified toxicity estimates can be used to define the "Negligible" range in a manner consistent with other existing U.S. acute health guidelines. It is important to appreciate, however, that the resulting low-level or Negligible hazard severity category is a range of toxicity estimates and that, in many cases, the upper bound of the Negligible hazard severity range is a reasonable objective. The lowest bound of the Negligible hazard severity range (i.e., PTE) represents an ideal goal that may not be practical, feasible, or even necessary for all chemical defense measures.

5.2.3 Specific Toxicity Values

The recommended chemical-specific toxicity ranges derived from the interim-military toxicity criteria should be grouped according to the hazard severity ranges described in Table 5-1. Despite certain data gaps, the information portrayed by the interim-acute military toxicity estimates, supplemented with additional extrapolation and adjustment, allows for a relatively comprehensive hazard characterization. This hazard characterization is more detailed than what can be described for most TICs. The recommended chemical-specific toxicity ranges for inhalation/ocular vapor exposure are presented in Table 5-2.

***NOTE:** Tables 5-2 and 5-3 display the specific range of vapor toxicity estimates in mg-min/m^3 for each agent and each hazard severity category. Guidance as to converting these values into concentration units is described below under Time Extrapolation.

For most applications, inhalation/ocular vapor exposure is the primary exposure pathway of concern. For those applications that require consideration of percutaneous vapor absorption or liquid contact, the recommended toxicity ranges for these pathways are presented in Tables 5-3 and 5-4. There is little experimental data exist from which to develop percutaneous vapor and liquid contact estimates; these latter values are, therefore, more uncertain than estimates for inhalation/ocular exposure pathways. Nevertheless, these groupings and associated hazard categories provide a consistent framework to select appropriate and consistent objectives for chemical defense applications. Future toxicological data resulting from ongoing research efforts

should be evaluated in terms of adjusting and refining the recommended toxicity values and ranges in Tables 5-2, 5-3, and 5-4.

5.2.4 Time Extrapolation and Unit Conversion

For many chemical defense applications, the interim-acute inhalation vapor toxicity estimates, which are presented in units of mg-min/m^3, must be converted to concentration units. According to the IDA report, the provided toxicity estimates were only for very short durations (e.g., 2 min for inhalation/ocular vapor exposures and 30 min for percutaneous vapor exposures), and a method of time extrapolation was not specifically advocated. This evaluation indicates inhalation vapor extrapolation for exposure durations up to 24 hours appears justified using appropriate models. Specifically, data that have become available since the IDA report publication and recently peer-reviewed by the NRC, provide a specific model for nerve agents: $C^2 \times t = k$ (ten-Berge equation) for exposure durations of 10 min to 8 hr, where C is concentration, t is time, and k a constant (for exposure durations between 8 hr and 24 hr, a straight-line extrapolation from the 8-hr values is recommended). For HD, the standard Haber's Law default ($C \times t = k$) is the most appropriate model (e.g., $n = 1$). To use these equations, one must first determine the specific k for a given population percentile. This must be derived from the original IDA data and probit slope to obtain the Ct (in mg-min/m^3) value for that particular percentile. This Ct is then converted to a 2-min C value by applying the ten-Berge equation with the appropriate n value, as described above, to obtain the specific k. Detailed information regarding time extrapolation is contained in Section 4.6.1 of this report. In addition, various conversions to provide concentration values for selected exposure durations of concern (i.e., 10 min, 1 hr, 8 hr, and 24 hr) have already been calculated and documented in Appendix E of this report.

5.2.5 Application of ORM and Toxicity Estimates to Chemical Defense Measures

The hazard severity ranges and recommended toxicity values in Tables 5-2 through 5-4, together with the described method for time extrapolation and conversion to concentration units, provide the specific criteria necessary for various chemical defense applications. To make these determinations, the types of chemical defense measures described in Chapter 3 of this report (e.g., modeling and planning, detection, and protection applications) were evaluated in terms of the associated requirements and operational needs, to include health impacts of concern and time durations of relevance. These are summarized in Table 5-5. Next, these needs and/or requirements (from Table 5-5) were specifically translated into the ORM hazard severity ranges and associated toxicity levels from Tables 5-2 through 5-4. Table 5-6 summarizes these specific hazard severity objectives with recommended toxicity ranges.

As a specific example of one such objective, the requirement for real-time, point-detection field devices should be to detect levels that are of "Negligible" severity (see Table 5-2). Based on the guidance provided and the current assumption that military personnel require 10 minutes to fully don protective gear, a reasonable recommendation would be that at a minimum the device should be able to detect an agent at the upper bound of the "Negligible" range for a 10-min exposure (as defined by the EC_{16} (mild) concentration in mg/m^3) and should provide results real-time within

seconds. Alternative goals might include detection at more protective levels such as the 10-min PTE or the 8 hr EC_{16} (mild) concentration. Basically, there will be various alternative specifications that may be acceptable as long as the resulting capability can be shown to detect within the "Negligible" hazard severity range for realistic exposure duration of concern.

5.2.6 Chemical Defense Measures for Homeland Security

In the above example, it is noted that the application of "male military" toxicity estimates may not seem appropriate for some applications. Ideally, for any specific Homeland Security or civilian application, the use of existing acute civilian vapor inhalation criteria for emergency response scenarios (known as AEGLs) should be preferentially used. However, it is realized that some applications (such as detector development) may have dual military and civilian uses. Therefore, a comparison of values derived from the DATSD-CBD set of vapor inhalation/ocular estimates relating to the NRC's AEGLs has been performed and shows that for the critical Negligible hazard severity range, there is good concordance with the AEGLs.

Specifically, the upper bound of the Negligible range for inhalation exposures, which is represented as an EC_{16} (mild) concentration, is in good concordance with the AEGL 2 values for nerve and HD agents (NRC/COT, 2003). AEGL 2 values for CWAs can be used as the primary protective action level as they represent levels below which there are not expected to be any significant (i.e., impairing or permanent) effects even among a mixed civilian population. To demonstrate a complete assessment, the NRC publishes AEGL 1 values to provide an estimation of the lowest end of the dose response curve where theoretically some very mild transient (non-impairing) effects may be noticed by a few of the most susceptible persons. An AEGL 1 value is often considered a notification level and not an action level. In comparison to the toxicity values derived from the DATSD-CBD acute interim-certified toxicity estimates, the estimated agent PTEs compare very closely with the AEGL 1 values. For those scenarios where an AEGL 3 might apply, it is noted that the AEGL 3 estimates are conservative (protective) estimates of severe effects and are all well below LC_{01} estimates for these agents; nerve agent AEGL 3 estimates fall in the upper "Marginal" hazard severity range, while HD AEGL 3 estimates are in the "Critical" hazard severity range.

The potential for delayed effects following agent exposure (particularly single, brief exposures) was also examined. Current NRC findings are summarized for HD in Section 4.1.1, and for nerve agents in Section 4.1.2. While mustard potentially induces carcinogenic effects at doses high enough to cause clinical casualties, there is no evidence that cancer would result from single, low-level exposures; therefore, the established military toxicity values are appropriate. The potential for G-nerve agents to cause delayed neurotoxic effects would be a concern only for survivors of exposures exceeding 10 x LD_{50}. Animal data for VX indicate that VX does not induce delayed neurotoxic effects even at multiple LD_{50}. For repeated exposures to Sarin concentrations not causing acute signs, some limited data collected from heat-stressed animals indicate differences from baseline in rat brain histochemistry and receptor-site density (Henderson, et. al., 2002). However, the clinical significance of these findings to humans is speculative.

Additional issues such as identification of pertinent PPE for non-military emergency responders will also need to be addressed with particular consideration of technical, regulatory, and risk acceptance criteria for these populations. Additional resources include USACHPPM, 2003b and Watson, et. al., 2003.

5.2.7 Application of AEGLs to Chemical Stockpile Emergency Preparedness Program

As an example of the application of AEGLs to scenarios involving potential civilian emergency/accidental exposures, the CSEPP Policy Paper Number 20, *Adoption of Acute Exposure Guidelines Levels (AEGLs)*, (CSEPP, 2003) mandates the use of the NRC published AEGLs for the nerve agent and HD. The CSEPP is jointly overseen by the Army and FEMA. The CSEPP program is designed to ensure that the state, local, and regional knowledge and resources are in place and capable of responding to a potential release of agent for one of the U.S. Army chemical agent stockpile sites. CSEPP Policy Paper Number 20 specifically describes how the AEGL 2 level is recommended as the primary action levels used for planning and response decision making. For similar Homeland Security plume modeling and response decision making, the recommendations of CSEPP Policy Paper Number 20 should be considered.

Table 5-2
Chemical Warfare Inhalation/Ocular Vapor Ct Toxicity Ranges Associated with ORM Hazard Categories
*** UNITS in mg-min/m^3 - see Notes re: conversion to concentration units mg/m^3**

AGENT Hazard Severity	GA	GB	GD	GF	VX	HD
CATASTROPHIC	>50	>25	>25	>25	>10	>100
CRITICAL	≤ 50 -- >1.0	≤ 25 -- >1.0	≤ 25 -- >0.4	≤ 25 -- >0.4	≤ 10 -- > 0.1	≤ 100 -- >16.8
MARGINAL	≤ 1.0 -- > 0.63	≤ 1.0 -- > 0.63	≤ 0.4 -- >0.27	≤ 0.4 -- >0.25	≤ 0.1 -- >0.06	≤ 16.8 -- >11.7
NEGLIGIBLE	≤ 0.63 - 0.034=PTE	≤ 0.63 - 0.034=PTE	≤ 0.27 -- 0.016=PTE	≤ 0.25 -- 0.014=PTE	≤ 0.06 -- 0.003 = PTE	≤ 11.7 -- 1.4 =PTE

* Conversion to concentration (mg/m^3) for durations up to 24 hours, use ten-Berge equations: for nerve agents: $C^2 \times t = k$ for durations of 10 min to 8 hr (for durations between 8 hr and 24 hr, use straight-line extrapolation from 8-hr values (i.e.,: $C^1 \times t = k$;); for HD, $C^1 \times t = k$); see para 5.2.4 for more details.

Table 5-3
Chemical Warfare Percutaneous Vapor (Absorption) Ct Toxicity Ranges Associated with ORM Hazard Categories
*** UNITS in mg-min/m^3 - see Notes re: conversion to concentration units mg/m^3**

AGENT / Hazard Severity	GA	GB	GD	GF	VX	HD
CATASTROPHIC	>9488	>7591	>2000	>1898	>25	>200
CRITICAL	≤ 9488 -- >2000	≤ 7591 -- >1200	≤ 2000 -- >300	≤ 1898 -- >300	≤ 25 -- >10	≤ 200 -- >25
MARGINAL	≤ 2000 - >1265-	≤ 1200 -- >759-	≤ 300 >205-	≤ 300 -- >190	≤ 10 -- >6.8	≤ 25 -- >11.7
NEGLIGIBLE	≤ 1265 333	≤ 759 -- 180	≤ 205 -- 45	≤ 190 -- 45	≤ 6.8 – 4	≤ 11.7 – 3

* Conversion to concentration (mg/m^3) for exposure durations of 10 min to 2 hr is estimated by assuming that *Ct* is constant. For civilian populations/other applications, risk-acceptance levels and associated bounds for negligible hazard may vary (see Watson, et. al., 2003).

Table 5-4
Chemical-Specific Liquid Toxicity Ranges Associated with ORM Hazard Categories
*** UNITS in mg/70 kg man - see Notes re: conversion to mg/cm^2**

AGENT / Hazard Severity	GA	GB	GD	GF	VX	HD
CATASTROPHIC	>900	>1000	>200	>200	>2.0	>600
CRITICAL	900 >150	1000 >150	200 >30	200 > 30	2.0 > 0.8	600 > 60
MARGINAL	150 >95	150 > 95	30 > 20	30 >19	0.8 > 0.55	60 > 28
NEGLIGIBLE	95 - 15	95 - 15	20 - 3	19 - 3	0.55 - 0.08	28 - 6

Estimates in mg/cm^2 can be determined by assuming 1.8 m^2 total body surface area of average male (per NRC/COT, 1997). For civilian populations/other applications, risk-acceptance levels and associated bounds for negligible hazard may vary (see Watson, et. al., 2003).

Table 5-5. Application of CW Agent Toxicity Criteria to Various Chemical Defense Measures

Application	Scenario/ Context	Objectives	Toxicity Criteria (for chemical-specific values see Table 5-1 and Appendix G)	Time/Duration	Notes, Alternatives, Limitations
Modeling and Simulation	Vulnerability Assessments, Hazard Prediction, and Casualty Estimation	Identify/ characterize all hazard severity (i.e., risk) levels	Use upper or midpoint of military toxicity estimates with highest statistical certainty (50^{th}, 84^{th}, 16^{th} percentile estimates) from within each severity category	Varies- extrapolate IDA-based toxicity estimates to fit longer time durations (up to 24 hrs for inh/oc, up to 2 hours for percutaneous) using chemical-specific time extrapolation models presented in section 4 (d) of this report	Quantified casualty estimates if needed should be noted with limited certainty For this level of gross prediction and planning, existing toxicity estimates and probit extrapolation are adequate for ORM decision making.
	FHP and OEH Hazard Surveillance	Identify/ characterize all exposures	All hazard severity categories; use lower bound* of negligible hazard range to identify lowest levels of exposures (*see information in Notes, Alternatives, Limitations)	Same as above	Alternatively AEGL 1 can be used as lowest level of potential exposure (as AEGLs are non-DOD, Federally approved criteria they have substantial credibility and address susceptible subpopulations); AEGL criteria should be used for Homeland Defense/Homeland Security modeling/planning/ prediction applications
Detection (Equipment and System specifications/ goals)	Point: "Alarm/ warn" real time	Identify presence at or above negligible levels	At a minimum should be able to detect levels at upper bound of negligible range	At a minimum (threshold) detect CW toxicity-based levels designated for 10 min exposures; longer (e.g. 1 hour for objective); results should be real-time (ie less than 10 min)	Alternatively AEGLs (such as AEGL 1 for 10 minute or longer) may be used as an objective
	Field Verification systems	Identify presence at or above negligible levels	At a minimum (threshold) should be able to detect levels at upper bound of negligible range (Inhalation Vapor)	Same as above	Alternatively AEGLs (such as AEGL 2 for threshold and AEGL1 for 10 min or longer) may be used as an objective
	Standoff: alarm/warn real time	Identify presence at or above marginal to negligible levels	At a minimum (threshold) should be able to detect levels within critical severity range; Ideally (obj) within bound of marginal (or even Negligible) range (Inhalation Vapor)	At a minimum (threshold) detect CW toxicity-based levels designated for 10 min exposures; longer (e.g., 1 hour for objective); results should be real time	AEGL 3 (10 min) is reasonable alternative threshold criteria for such systems that are designed for gross identification of plumes and which would provide substantial time to don protective gear.
	Surface detection	Identify presence at or above negligible levels	At a minimum (threshold) should be able to detect levels within marginal severity; Ideally (obj) within bounds of Negligible range (Liquid)	For real-time field detection results should be obtained for minimum 30-min exposures	No equivalent Federal (civilian) criteria exist for liquid or percutaneous vapor exposure routes. The established threshold "low-level" estimates for liquid (percutaneous) exposures are particularly uncertain and were derived using an unprecedented approach (as no establish model exists).
Protection (future equipment objectives)	Individual (mask, respiratory protection)	Prevent/ minimize exposure to ambient CW vapors down to negligible levels	Should be able to provide protection against lethal levels to levels within negligible range (at minimum upper bound, goal lower bound) (Inhalation Vapor)	Should maintain negligible range exposures for minimum of 10 min (threshold); ideally (obj) for longer (e.g., 1 hr or 8 hrs)	AEGL 1 criteria are alternative goals for testing break though limits. Particularly desired for civilian applications.
	Individual (suit, ensemble)	Prevent/ minimize exposure to ambient CW vapors and liquids down to negligible levels	Should be able to provide protection against lethal levels to levels within negligible range (at minimum upper bound, goal lower bound*) (Percutaneous Vapor)	Should be able to maintain negligible range exposures for mi nimum of one hour (threshold); ideally (obj) for longer	*Lower-bound estimates are recommended criteria particularly for assessing breakthrough to particularly susceptible body regions (such as head, neck, groin, and armpit)
	Collective Protection	Prevent/ minimize exposure to ambient CW vapors/liquids to negligible levels	Should be able to provide protection against lethal levels to levels within negligible range (Inhalation Vapor)	Should maintain negligible range exposures for minimum of 1 hr (threshold); ideally (obj) for longer (e.g., 8 hrs – 24 hrs)	Should maintain negligible range exposures for minimum of 1 hr (threshold); ideally (obj) for longer (e.g., 8 hrs – 24 hrs)
Decontam-ination	Id residual hazards, de-MOPP, re-use and reentry	Determine residual contamination/ validate decon	See point, verification, and surface "detection" criteria above. Also see Table 3-1.		
Medical Treatment	Pre-treatment and Post Exposure	Reduce/eliminate effects from lethal agent exposures with minimal side effects	Should be able to effectively accommodate lethal exposures reflecting worst case scenarios: > LD50 or LCt50	Not applicable	Current objectives (Section 3.f) are based on Textbook of Military Medicine (Chapter 6) criteria that describe effective pretreatment/ therapy measures as that which would enable persons to survive 5 x LD50. Therapy alone has been determined effective if it can protect against 2 x LD50. However, therapy or pretreatment that together or alone provide protection (ensure survivability and no disabling effects) for any exposures above the LD50 may have some merit.

Table 5-6. General Hazard Severity Objectives for Various Chemical Defense Measures

Chemical Defense Measure	Specific Application	Key Exposure (primary)[a]	Hazard Severity Categories of Primary Interest
Modeling and Simulation	Threat Analyses-Casualty Estimation	inh/oc VAPOR	Demonstrate **all** (*gross estimation)*
	FHP/Occupational Environmental Surveillance and reporting	inh/oc VAPOR	Demonstrate **all** (*to **lower bound** of Negligible range for exposure documentation)*
Contamination Avoidance/ Detection[b]	Stand-off	inh/oc VAPOR liquid	Identify at a minimum **Critical-Marginal**
	Liquid	liquid	Identify at a minimum **Critical - Marginal**
	Point – field (alarm)	inh/oc VAPOR	Identify **Negligible**
	Point (verification)	inh/oc VAPOR	Identify **Negligible**
Decontamination	Varies (see Table 3-1 USACHPPM report)	liquid, VAPOR	**Varies** (see Table 3-1 USACHPPM report); parallels Detection capabilities
Protection	Individual- respirator	inh/oc VAPOR	Protect to **Negligible**
	Individual-suit	perc VAPOR	Protect to **Negligible**
	Collective	inh/oc VAPOR	Protect to **Negligible**
Medical interventions		liquid, VAPOR	Protect against **Catastrophic**[c]

[a] inh = inhalation exposure; oc = ocular exposure.

[b] Specific detection goals should be based on a concentration level that corresponds to a specific exposure duration of concern; detection results should be available real-time/well before end of exposure duration.

[c] The objective is to develop medical countermeasures that can adequately ensure survivability of persons exposed to maximum exposures (2 – 5 times the LC or LC_{50}).

5.3 POINT OF CONTACT INFORMATION

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APPENDIX A

REFERENCES

Anderson, J.S. 1942. The effect of mustard gas vapour on eyes under Indian hot weather conditions. CDRE Report No. 241. Chemical Defense Research Establishment (India).

Anthony, J.S., M.V. Haley, J.H. Manthei, R.A. Way, D.C. Burnett, B.P. Gaviola, D.R. Sommerville, R.B. Crosier, R.J. Mioduszewski, E.M. Jakubowski, J.L. Montgomery, and S.A. Thomson. 2002. *Inhalation toxicity of GF vapor in rats as a function of exposure concentration and duration and its potency comparison to GB*. Late-breaking Poster presented at 41st Annual Meeting of the Society of Toxicology, Nashville, TN, 21 March 2002.

Baker, D.J., and E.M. Sedgwick. 1996. "Single fibre electromyographic changes in man after organophosphate exposure." *Hum. Exp. Toxicol*. 15:369-375.

Blewett, W.K. 1986. "Tactical weapons: Is mustard still king?" *NBC Defense Technology International.* 1: 64-66.

Chanda, S.M., T.L. Lassiter, V.C. Moser, S. Barone, Jr., and S. Padilla. 2002. Tissue carboxylesterases and chlorpyrifos toxicity in the developing rat. HERA 8: 75-90.

Costa, L.G., T.B. Cole, and C.E. Furlong. 2003. Polymorphisms of paraoxonase (PON1) and their significance in clinical toxicology of organophosphates. Clinical Toxicol. 41: 37-45.

Chemical Stockpile Emergency Preparedness Program (CSEPP), 2003. CSEPP Policy Paper Number 20 (Revised): Adoption of Acute Exposure Guideline Levels (AEGLs). Department of the Army, Federal Emergency Management Agency, Chemical Stockpile Emergency Preparedness Program, 24 February 2003.

Crosier, R. B. 2003. Mathematical limits on differences between a population and a subpopulation. ECBC-TR-337. Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD.

DATSD-CBD (Assistant to the Secretary of Defense–Chemical and Biological Defense). Memorandum, DATSD-CBD, SUBJECT: *Interim Certification of Chemical and Biological Data,* 27 December 2001. (Assistant to the Secretary of Defense, 3050 Defense Pentagon, Washington, D.C.).

Davies, H.G., R.J. Richter, M. Keifer, C.A. Broomfield, J. Sowalla, and C.E. Furlong. 1996. The effect of human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin. Nat. Genet. 14: 334-336.

Department of the Army (DA). 1974. Chemical agent data sheets, vol. 1. Edgewood Arsenal Special Report, EO-SR-74001. U.S. Department of the Army, Edgewood Arsenal, Aberdeen Proving Ground, MD.

Department of the Army (DA). 1990. Field Manual (FM 3-9), *Potential Military Chemical/Biological Agents and Compounds*. (NAVFAC P-467, AFR 355-7), Headquarters, Department of the Army, Department of the Navy, Department of the Air Force, Washington, DC (12 December, 1990). (Distribution Restriction: Distribution is authorized to U.S. government agencies only to protect technical or operational information from automatic dissemination under the International Exchange Program or by other means. This determination was made 1 January 1991. Other requests for this document will be referred to Commandant, U.S. Army Chemical School, ATTN: ATZA-CM-NF, Fort McClellann, AL 36205-5020.)

Department of the Army (DA). 1997. Field Manual (FM) 101-5-1, *Operational Terms and Graphics,* September 1997.

Department of the Army (DA). 1997. *Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare*. Chapter 6, "Pretreatment for Nerve Agent Exposure." Peer Reviewed by Michael A. Dunn, M.D., FACP; Brennie E. Hackley, Jr., PhD.; and Frederick R. Sidell, M.D. Last Revision Date: May 1997.
http://www.vnh.org/MedAspChemBioWar/

Department of the Army (DA). 1998. Field Manual (FM) 100-14, *Risk Management*, April 1998.

Department of the Army (DA). 2000. Field Manual (FM) 4-02.17, *Preventive Medicine Services,* August 2000.

Department of the Army (DA). 2001. HQDA Letter 1-01-1, *Force Health Protection (FHP): Occupational and Environmental Health (OEH) Threats*, 28 July 2003.

Department of the Army (DA). 2001. Army Field Manual FM 3-100.12/MCRP 5-12.1C/NTTP 5-03.5/AFTTP(I) 3-2.30, *Multi-Service Tactics, Techniques and Procedures for Risk Management.*

Department of the Army (DA). 2003a. Pamphlet 40-8 (DA PAM 40-8). *Occupational Health Guidelines for the Evaluation and Control of Occupational Exposure to Nerve Agents GA, GB, GD, GF and VX*. Department of the Army Headquarters, Department of the Army, Washington, DC (February 2003 draft revision).

Department of the Army (DA). 2003b. Pamphlet 40-173 (DA PAM 40-173). *Occupational Health Guidelines for the Evaluation and Control of Occupational Exposure to Mustard Agents H, HD, and HT*. Department of the Army Headquarters, Department of the Army, Washington, DC (February 2003 draft revision).

Department of the Army (DA). 2003c. Field Manual 4-02, *Force Health Protection in a Global Environment.*

Department of Defense (DOD). 1999. *Strategy to Address Low-Level Exposures to Chemical Warfare Agents*, 1999 (response to Congress).

Department of Defense (DOD). 2002. *U.S. Demolition Operations at Khamisiyah, Final Report*. April 16, 2002. Department of Health Affairs.
http://www.gulflink.osd.mil/khamisiyah_iii/

Department of Defense (DOD). 2003. *Low-Level Chemical Warfare Agents (CWAs) Exposure Research Master Plan.* Final Draft. (DASTD-CBD). Submitted to NRC-COT.

Duffy, F.H., J.L. Burchfiel, P.H. Bartels, M. Gaon, and V.M. Sim. 1979. "Long-term effects of an organophosphate upon the human electroencephalogram." *Toxicol. Appl. Pharmacol*. 47:161-176.

Duffy, F.H., and J.L. Burchfiel. 1980. "Long-term effects of the organophosphate sarin on EEGs in monkeys and humans." *Neurotoxicology* 1:667-689.

Duncan, E.J.S., A. Brown, P. Lundy, T.W. Sawyer, M. Hamilton, I. Hill, and J.D. Conley. 2002. "Site-specific percutaneous absorption of methyl salicylate and VX in domestic swine." *J. Appl. Toxicol.* 22: 141-148.

Federal Register, Vol. 68, No. 196, pp. 58348-58351, "Final Recommendations for Protecting Human Health From Potential Adverse Effects of Exposure to Agents GA (Tabun), GB (Sarin), and VX." October 9, 2003.

Federal Register, Vol. 69, No. 85, pp. 24164-24168, "Interim Recommendations for Airborne Exposure Limits for Chemical Warfare Agents H and HD (Sulfur Mustard)."
3 May, 2004.

Freeman, G., F.N. Marzulli, A.B. Craig, et al. 1954. *The toxicity of liquid GA applied to the skin of man*. MLRR-50, Chemical Corps Medical Laboratory Research Report, Army Chemical Center, MD. Unclassified Report AD 029 550 (March 1954).

Furlong, C.E., W-F. Li, D.M. Shih, A.J. Lusis, R.J. Richter, and L.G. Costa 2002. *Genetic factors in susceptibility: Serum PON1 variation between individuals and species*.
HERA 8: 31-43.

Gilchrist, H.L. 1928. *A Comparative Study of World War Casualties from Gas and Other Weapons*. U.S. Government Printing Office, Washington, D.C.

Grob, D, B. Zeiglker, G. Saltzer and G.I. Johnson. 1953. *Further observations on the effects in man of methyl isopropyl flurorophosphonite (GB): effects of percutaneous absorption through intact and abraded skin*. Chemical Corps Medical Laboratories Report, MLCR No. 14. Johns Hopkins University, Baltimore, MD.

Grotte, J.H., and L.I. Yang. 2001. *Report of the Workshop on Chemical Agent Toxicity for Acute Effects*. Institute for Defense Analyses, 11-12 May, 1998. IDA Document D-2176, Institute for Defense Analyses, 1801 N. Beauregard St., Alexandria, VA.

Haber, F. (1924). Zur geschichte des gaskrieges, in *Funf Vortrage aus den Fahren*, 1920-1923, pp. 23-29, Verlag von Fulius Springer, Berlin.

Harvey, J.C. 1952. *Clinical observations on volunteers exposed to concentrations of GB*. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52). Army Chemical Center, MD.

Hayes, W.J. 1982. Pesticides Studies in Man. William and Wilkins, Baltimore, MD

Henderson, R.F., E.B. Barr, W. B. Blackwell, C. R. Clark, C. A. Conn, R. Kalra, T.H. March, M.L. Sopori, Y. Tesfaigzi, M. G. Ménache, and D.C. Mash. 2002. "Response of rats to low levels of sarin." *Toxicol. Appl. Pharm*. 184: 67-76.

Institute of Medicine (IOM). 1993. *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite.* Pechura, C.M., and D.P. Rall (eds). Committee to Survey the Health Effects of Mustard Gas and Lewisite, Division of Health Promotion and Disease Prevention, National Academy Press, Washington, DC.

Johns, R.J. 1952. *The effect of low concentrations of GB on the human eye*. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD.

Joint Publication 4-02, (JP 4-02, 2001). 2001. Doctrine for Health Service Support in Joint Operations.

Joint Staff Central Command (CENTCOM), Joint Theater Personnel Roster (JTPR). 2001-2003. Personnel Services Directorate provided by 3rd Army Personnel Command (PERSCOM) to USACHPPM in February 2003. (Describes basic personnel information regarding forces and/or units deployed to CENTCOM region during 2001-2003 timefrime. Basic gender statistics were obtained from the provided dataset by W. Wortman of USACHPPM.)

Joint Staff Central Command (CENTCOM), Tactical Personnel System (TPS). February 2003. TPS v2.2 output data provided basic personnel "manifest" information from which personnel gender statistics for recent deployments (e.g., Operation Iraqi Freedom) estimated by W. Wortman, USACHPPM.

Kleinbaum, D.C., L.L. Kupper, and K.E. Miller. 1988. *Applied Regression Analysis and Other Multivariate Methods*. Duxbury Press, Belmont, CA.

Kumar, O. and R. Vijayaraghavan. 1998. "Effect of sulphur mustard inhalation exposure on some urinary variables in mice." *J. Appl. Toxicol*. 18: 257-259.

Landahl, H.D., 1945. A Formal Analysis of the Action of Liquid Vesicants on Bare Skin. University of Chicago Toxicity Laboratory Report No. 50. U. of Chicago, Chicago, IL.

MCM, 2002a. Memorandum, MCM-0006-02, *Joint Chiefs of Staff, Updated Procedures for Deployment Health Surveillance and Readiness*, 1 February 2002 http://www.dtic.mil/doctrine/jel/cjcsd/cjcsi/mcm6_02.pdf

MCM, 2002b. Memorandum, MCM-0026-02, *Chemical Warfare (CW) Agent Exposure Planning Guidance*, 29 April 2002.

Mioduszewski, R.J., J. Manthei, R. Way, D. Burnett, B. Gaviola, W. Muse, S. Thomson, D. Sommerville, and R. Crosier. 2000. *Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration*. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000), The Hague, Netherlands (May 21-24, 2000).

Mioduszewski, R.J., J. Manthei, R. Way, D. Burnett, B. Gaviola, W. Muse, J. Anthony, D. Durst, D. Sommerville, R. Crosier, S. Thomson, and C. Crouse. 2001. *ECBC Low Level Operational Toxicology Program: Phase IB Inhalation toxicity of sarin vapor in rats as a function of exposure concentration and duration.* ECBC-TR-183, Edgewood Research Development and Engineering Center, Aberdeen Proving Ground, MD (August 2001).

Mioduszewski, R.J., J. Manthei, R. Way, D. Burnett, B. Gaviola, W. Muse, S. Thomson, D. Sommerville, and R. Crosier. 2002a. "Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats." *Toxicol. Sci*. 66: 176-184.

Mioduszewski, R.J., J. Manthei, R. Way, D. Burnett, B. Gaviola, W. Muse, S. Thomson, D. Sommerville, R. Crosier, J. Scotto, D. McCaskey, C. Crous, and K. Matson. 2002b. *Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size*. ECBC-TR-235. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD. (May 2002).

Morgan, D.P. 1989. *Recognition and Management of Pesticide Poisonings*. 4th edition. EPA-540/9-88-001. U.S. Environmental Protection Agency, Washington, D.C.

Munro, NB, KR Ambrose, and AP Watson, 1994. "Toxicity of the organophosphate chemical warfare agents GA, GB and VX: Implications for public protection." *Environ. Health Persp.* 102: 18-38.

National Research Council, Board on Army Science and Technology (NRC/BAST). 1997. *Technical Assessment of the Man-in-Simulant Test (MIST) Program*. Assessment of the Standing Committee on Program and Technical Review of the U.S. Army Chemical and Biological Defense Command, Board on Army Science and Technology, National Research Council. National Academy Press, Washington, D.C.

National Research Council, Committee on Toxicology (NRC/COT). 1997. *Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents*, Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, Committee on Toxicology, National Research Council. National Academy Press, Washington, DC.

National Research Council (Institute of Medicine). 1999. *Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response*. National Academy Press, Washington, DC.

National Research Council, Committee on Toxicology (NRC/COT). 2001. *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals*. Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council. The National Academy Press, Washington, DC.

National Research Council, Committee on Toxicology (NRC/COT). 2003. *Acute Exposure Guideline Levels Selected Airborne Chemicals, Volume 3*. Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council. National Academy Press, Washington, DC.

National Research Council, Committee on Toxicology (NRC/COT). 2004. *Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel*. Subcommittee on the Toxicological Risks to Deployed Military Personnel, Committee on Toxicology, National Research Council. National Academy Press, Washington, DC.

Oak Ridge National Laboratory (ORNL). 2003. *Evaluation of Chemical Warfare Agent Percutaneous Vapor Toxicity: Derivation of Toxicity Guidelines for Assessing Chemical Protective Ensembles*. ORNL/TM-2003/180. (Oak Ridge National Laboratory, Oak Ridge, TN).

Papirmeister, B., A.J. Feister, S.I. Robinson, and R.D. Ford. 1991. *Medical Defense Against Mustard Gas: Toxic Mechanisms and Pharmacological Implications.* CRC Press, Boca Raton, FL.

Reutter-Wade (R-W) (Reutter, S.A., and J.V. Wade. 1994. "Table 1. Summary of Existing and Recommended Estimates (U)," unclassified summary table from *Review of existing toxicity data and human estimates for selected chemical agents and recommended human toxicity estimates appropriate for defending the soldier*. ERDEC-SP-018. U.S. Department of the Army, Edgewood Research Development and Engineering Center, Aberdeen Proving Ground, MD (Secret report).

Rostker, B. 1999. *Information Paper: M256 Series Chemical Agent Detector Kit*. Office of the Special Assistant of Gulf War Illnesses, Department of Defense, The Pentagon. (http://www.gulflink.osd.mil/m256/)

Sidell, FR, 1992. "Clinical considerations in nerve agent intoxication," pp. 155-194 in Somani, SM (ed), *Chemical Warfare Agents*. Academic Press, New York, NY.

Sidell, F.R., E.T. Takafuji, and D.R. Franz (eds). 1997. *Medical Aspects of Chemical and Biological Warfare*. Published by the Office of The Surgeon General, at TBMM Publications, Borden Institute, Walter Reed Army Medical Center, Washington, DC 20307-5000.

Sim, V.M., and J.L. Stubbs. 1960. *VX percutaneous studies in man (U)*. CRDLR 3015, AD 318533. US Army Chemical Research and Development Laboratories Technical Report, Army Chemical Center, MD.

Sim, V.M. 1962. *Variability of different intact human-skin sites to the penetration of VX.* CRDLR 3122, AD 271163, U.S. Army Chemical Research and Development Laboratories Technical Report, Army Chemical Center, MD.

Smith, W.J. 2002. "Vesicant agents and antivesicant medical countermeasures: Clinical toxicology and psychological implications." *Military Psychology* 14(2): 145-157.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. "Concentration-time mortality response relationship of irritant and systemically acting vapours and gases." *J. Hazard. Materials,* 13:301-309.

The Technical Cooperation Program (TTCP). 1981. Minutes of the 15-16 October 1981 TTCP Subgroup E Technical Panel meeting. http://www.dtic.mil/ttcp/overview.htm

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). 1999. Information for Combat Developers on Performance Effects From Exposure to Chemical Warfare Agents. USACHPPM, Aberdeen Proving Ground, MD 21010 (March 1999). Edited by Jesse J. Barkley, Jr. (U.S. Army Center for Health Promotion and Preventive Medicine, ATTN: MCHB-TS (S. Kistner), 5158 Blackhawk Road, Aberdeen Proving Ground, MD 21010-5403.)

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Technical Guide 248. 2001. *Guide for Deployment Military Personnel on Health Risk Management*. USACHPPM, Aberdeen Proving Ground, MD 21010 (August 2001). http://chppm-www.apgea.army.mil/documents/TG/TECHGUID/TG248.pdf

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Technical Guide 244. 2002. *The Medical NBC Battlebook*. USACHPPM, Aberdeen Proving, Ground, MD 21010 (August 2002).

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). 2003a. *Reference Document for USACHPPM Technical Guide 230, Version 1.3 May 2003.* USACHPPM, Aberdeen Proving Ground, MD 21010. http://chppm-www.apgea.army.mil/documents/TG/TECHGUID/TG230RD.pdf

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). 2003b. Technical Guide 275, *Personal Protection Equipment for Military Medical Treatment Facility Personnel Handling Casualties from Weapons of Mass Destruction and Terrorism Events*. USACHPPM, Aberdeen Proving Ground, MD 21010 (August 2003). http://chppm-www.apgea.army.mil/documents/TG/TECHGUID/TG275new.pdf

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Technical Guide 230. 2004. *Chemical Exposure Guidelines for Deployed Military Personnel, Version 1.3, May 2003- with January 2004 Addendum*. USACHPPM, Aberdeen Proving Ground, MD 21010. http://chppm-www.apgea.army.mil/documents/TG/TECHGUID/TG230.pdf

U.S. Environmental Protection Agency (USEPA). 1989. *Risk Assessment Guidance for Superfund, Volume 1 – Human Health Evaluation Manual*; EPA/540/1-89/002; Office of Emergency and Remedial Response, USEPA, Washington, D.C.

U.S. Environmental Protection Agency (USEPA). 1994. Methods for the Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry; EPA/600/8-90/066F; Office of Research and Development, USEPA, Washington, D.C.

U.S. Environmental Protection Agency (USEPA). 2000. Office of Pesticide Programs science policy on the use of data on cholinesterase inhibition for risk assessment of organophosphorus and carbamate pesticides. Office of Pesticide Programs, USEPA, Washington, DC (August 18, 2000).

van Helden, H.P.M., J.P. Langenberg, and H.P. Benschop. 2001. *Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, and Performance Incapacitation*. Award No. DAMD17-97-1-7360. TNO Prins Maurits Laboratory, Final Report to the U.S. Army Medical Research and Materiel Command, Fort Detrick, MD, April 2001.
van Helden, H.P.M. H.C. Trap, W.C. Kuijpers, B. Groen, J.P. Oostdijk, R.A.P. Vanwersch, I.H.C. Philippens, J.P. Langenberg, and H.P. Benschop. 2002. *Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Level, and Performance-Incapacitation*. Research and Technology Organisation (RTO) Meeting Proceedings 75, Operational Medical Issues in Chemical and Biological Defense (RTO-MP-075, AC/323 (HFM-060) TP/37) held in Estoril, Portugal, 14-17 May 2001. North Atlantic Treaty Organisation,

Research and Technology Organisation, BP 25, 7 Rue Ancelle, F-92201 Neuilly-sur-Seine CEDEX, France.

Watson, A., D. Opresko, and V. Hauschild. 2003. *Evaluation of chemical warfare agent percutaneous vapor toxicity: Derivation of toxicity guidelines for assessing chemical protective ensembles*. ORNL/TM-2003/180. Oak Ridge National Laboratory, Oak Ridge, TN.

Wills, J.H. 1972. "The measurement and significance of changes in the cholinesterase activities of erythrocytes and plasma in man and animals." *CRC Crit. Rev. Toxicol*. 1:153-202.

Wormser, U., B. Brodsky, and A. Sintov. 2002. "Skin toxicokinetics of mustard gas in the guinea pig: Effect of hypochlorite and safety aspects." *Arch. Toxicol*. 76 (9): 517-522.

Yamasaki, Y., K. Sakamoto, H. Watada, Y. Kajimoto, and M. Hori. 1997. "The Arg 192 isoform of paraoxonase with low sarin-hyrolyzing activity is dominant in the Japanese." *Japan. Hum. Genet*. 10: 67-68.

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APPENDIX B
INSTITUTE OF DEFENSE ANALYSIS (IDA) REPORT

AND

REUTTER-WADE, TABLE 1. SUMMARY OF EXISTING AND RECOMMENDED ESTIMATES (U)

This Appendix includes a full copy of—

- Grotte and Yang, 2001. Institute for Defense Analyses (IDA), Report of the Workshop on Chemical Agent Toxicity for Acute Effects, May 11-12, 1998.

and, on page B-27:

- Unclassified Table 1 from the Reutter-Wade, 1994 classified report that served as the initial basis for the follow-on analyses resulting in the interim-certified military acute toxicity estimates that are documented in the IDA report (Reutter-Wade (R-W), Table 1. Summary of Existing and Recommended Estimates (U), 1994).

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IDA

INSTITUTE FOR DEFENSE ANALYSES

Report of the Workshop on Chemical Agent Toxicity for Acute Effects

Institute for Defense Analyses
May 11-12, 1998

Jeffrey H. Grotte
Lynn I. Yang

June 2001

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CHPPM Report No. 47-EM-5863-04, May 04

INSTITUTE FOR DEFENSE ANALYSES

IDA Document D-2176

Report of the Workshop on Chemical Agent Toxicity for Acute Effects

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Jeffrey H. Grotte
Lynn I. Yang

PREFACE

This document was prepared by the Institute for Defense Analyses in partial fulfillment of the Task Order "Support for Quadrennial Defense Review (QDR) — Analysis of Defense Against Chemical/Biological Weapons," sponsored by the Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs.

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CONTENTS

TABLES

A. INTRODUCTION

The potential use of chemical agents against US forces is becoming a prominent concern. This is true not only in major theaters of war, but also in lesser contingencies and operations other than war where the US military could face insurgents or terrorists with access to these deadly materials. For US forces to have the best defenses against chemical agents, those responsible for developing these defenses must have the best available estimates of agent toxicity and associated risks.

There is an inherent tension between the stringency of protective measures and the operational burden of implementing them. Because of this, defenses against chemical agents typically strive to ensure sufficient protection while minimizing disruption to military operations. If toxicity—here used to mean the median lethal or effective dosage or dose, and the degree of variation in human response—is underestimated, defenses may not provide sufficient protection. Unacceptable chemical casualties could occur. If toxicity is overestimated, protective measures could be overly burdensome (and, perhaps, overly expensive). Force effectiveness could be diminished and unacceptable additional conventional casualties could occur.

Estimating chemical agent toxicity is, however, a challenging scientific effort that draws on animal studies and their extrapolation to humans, limited direct data on human reaction to these agents, and even more limited data regarding the results of chemical agent use on the battlefield. Various studies have produced different toxicity estimates over the years, and there have been generally accepted estimates that have been documented in Army field manuals and other official sources. In 1994, the US Army Chemical Defense Equipment Process Action Team published the results of an extensive reexamination of the sources of toxicity estimates for the agents GA, GB, GD, GF, VX, and HD. This report is generally referred to as the Reutter-Wade report [1]; it recommended human toxicity estimates appropriate for defending the soldier. Many of the recommended estimates were markedly different from those that had been accepted for decades.

This report was carefully reviewed. One review, by the Army Science Board [2], recommended that the Reutter-Wade estimates be adopted on an interim basis while further data were collected. Another, by the Committee on Toxicity of the National Research Council [3], proposed accepting some estimates on an interim basis, while

suggesting that others be raised or lowered based on their [the Committee's] opinion of the quality of existing data. Moreover, some individuals in the chemical defense community felt, based on their own experience and on previous reviews, that some of the Reutter-Wade estimates were not as valid as other estimates.

Because of the importance of these estimates to those responsible for developing chemical defense equipment, estimating medical requirements, and analyzing the effects of chemical weapons against US forces, Mr. Walter Hollis, Deputy Under Secretary of the Army for Operations Research, asked the Joint NBC Board Secretariat to convene a workshop to (1) reach a consensus on interim toxicity parameters for the six agents mentioned above, (2) specify guidelines for their use, and (3) identify high priority areas for future work to improve these estimates. This workshop was held May 11 and 12, 1998, at the Institute for Defense Analyses, and included representation from the chemical defense community, the medical community, the analytical community, three Services, the Joint Service Integration Group, and the Joint Service Material Group (workshop participants are listed in the Appendix). This paper summarizes the results of this workshop.

B. WORKSHOP RESULTS

1. Scope

In order to keep the problem tractable, the sponsor requested that the workshop focus on:

- Acute effects, as opposed to chronic effects or effects from low-level exposures;
- 70 kilogram male soldiers, as opposed to civilians or female military personnel;
- Military scenarios, as opposed to use against civilians; and
- Neat versions of the six agents, as opposed to other agents or modified versions of the six agents.

All other variations are recognized as important, but there are substantial data shortfalls with regard to these situations; they will be identified below as areas where further work needs to be done.

2. Toxicity Estimates

The workshop participants discussed each toxicity estimate at length, and consensus was reached on each one. Tables 1 through 6 summarize the consensus values, along with some of the caveats that arose during the discussion. Each estimate comprises two values, a median and a probit slope. Notes that summarize key issues raised during the discussions follow the tables. Numbers identifying the notes are given in braces in the tables.

Units for doses are milligrams. Percutaneous liquid values are for the total applied dose to a 70-kg man (the applied dose is assumed to be completely absorbed). All percutaneous vapor and small particle aerosol values pertain to 30-minute exposures for individuals without clothing. For nerve agents, percutaneous vapor exposure estimates are for masked soldiers with eye protection.

Units for dosages are milligram-minutes/meter^3. All inhalation values pertain to two-minute exposures and are for a minute volume (MV) of 15 liters.

Table 1. GA Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
GA	LCt50	Percutaneous vapor	15000/5 {1}
GA	LCt50	Inhalation vapor	70/12
GA	ECt50, threshold {2}	Percutaneous vapor	2000/5 {3}
GA	ECt50, severe {4}	Percutaneous vapor	12000/5 {3}
GA	ECt50, severe {4}	Inhalation vapor	50/10
GA	ECt50, mild {5}	Inhalation vapor	1/5 {6}{14}
GA	LD50	Percutaneous liquid	1500/5 {1}
GA	ED50, severe {4}	Percutaneous liquid	900/5 {1}

Table 2. GB Toxicity Values [1]

Agent	Parameter	Route of Entry	Value/Probit Slope
GB	LCt50	Percutaneous vapor	12000/5{7}
GB	LCt50	Inhalation vapor	35/12
GB	ECt50, threshold {2}	Percutaneous vapor	1200/5 {3}
GB	ECt50, severe {4}	Percutaneous vapor	8000/5 {3}{8}
GB	ECt50, severe {4}	Inhalation vapor	25/10
GB	ECt50, mild {5}	Inhalation vapor	1/5 {9}{14}
GB	LD50	Percutaneous liquid	1700/5 {1}
GB	ED50, severe {4}	Percutaneous liquid	1000/5 {1}

[1] An objection was raised following the conclusion of the workshop regarding the derivation of the GB inhalation LCT50. Because this value is used as the basis for other G-agent values, its accuracy is critical. IDA's examination of this objection is summarized in a memorandum for the record (Appendix A). Although the objection was valid, there is sufficient evidence to warrant retaining the Reutter-Wade value and, hence, the workshop recommendation.

Table 3. GD Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
GD	LCt50	Percutaneous vapor	3000/6 {10}
GD	LCt50	Inhalation vapor	35/12
GD	ECt50, threshold {2}	Percutaneous vapor	300/6 {3}
GD	ECt50, severe {4}	Percutaneous vapor	2000/6 {3}{11}
GD	ECt50, severe {4}	Inhalation vapor	25/10
GD	ECt50, mild {5}	Inhalation vapor	0.4/6 {3}{14}
GD	LD50	Percutaneous liquid	350/6 {1}
GD	ED50, severe {4}	Percutaneous liquid	200/6 {1}

Table 4. GF Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
GF	LCt50	Percutaneous vapor	3000/5 {10}
GF	LCt50	Inhalation vapor	35/12
GF	ECt50, threshold {2}	Percutaneous vapor	300/5
GF	ECt50, severe {4}	Percutaneous vapor	2000/5
GF	ECt50, severe {4}	Inhalation vapor	25/10
GF	ECt50, mild {5}	Inhalation vapor	0.4/5 {14}
GF	LD50	Percutaneous liquid	350/5 {1}
GF	ED50, severe {4}	Percutaneous liquid	200/5 {1}

Table 5. VX Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
VX	LCt50	Percutaneous vapor	150/6 {12}
VX	LCt50	Inhalation vapor	15/6 {1}
VX	ECt50, threshold {2}	Percutaneous vapor	10/6 {3}
VX	ECt50, severe {4}	Percutaneous vapor	25/6
VX	ECt50, severe {4}	Inhalation vapor	10/6
VX	ECt50, mild {5}	Inhalation vapor	0.1/4 {3}{14}
VX	LD50	Percutaneous liquid	5/6 {1}
VX	ED50, severe {4}	Percutaneous liquid	2/6 {1}

Table 6. HD Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
HD	LCt50	Percutaneous vapor	10000/7 {15}
HD	LCt50	Inhalation vapor	1000/6 {1}{16}
HD	ECt50, threshold, moderate temperature {13}	Percutaneous vapor	50/3 {17}
HD	ECt50, threshold, hot temperature {13}	Percutaneous vapor	25/3 {17}
HD	ECt50, severe, moderate temperature {18}	Percutaneous vapor	500/3 {17}
HD	ECt50, severe, hot temperature {18}	Percutaneous vapor	200/3 {17}
HD	ECt50, severe {19}	Ocular vapor	100/3 {3}
HD	ECt50, mild {19}	Ocular vapor	25/3 {3}
HD	LD50	Percutaneous liquid	1400/7 {1}
HD	ED50, severe {18}	Percutaneous liquid	600/3 {1}{20}

Notes for Tables 1-6

(1) The workshop participants agreed that data did not support much precision with regard to probit slope. Hence, the Reutter-Wade value was rounded to a whole number.
(2) As used here, threshold refers to a slight ChE inhibition.
(3) There are no data to justify a probit slope, but the recommended value can be used as an interim value until such time that data are available.
(4) For organophosphate nerve agents, severe effects are systemic, similar to lethal effects.
(5) Inhalation vapor ECt's include ocular exposure. The term "mild" refers to a level of symptom (ocular, rhinorrhea, and/or chest tightness) that might be noticed in the field.
(6) There were very few data to support an estimate of this value (or of the corresponding value for GB, from which values for GA were frequently derived). Given the lack of data and the recommendation of the NRC to raise the value provided by Reutter-Wade, the workshop accepted 1.0 as an interim value, with a probit slope of 5. These values should not be used under conditions where this effects curve crosses a more severe effects curve.
(7) There was considerable discussion regarding whether the value in Reutter-Wade was consistent with poorly-documented anecdotal field experience, which appears to argue for a larger value. Although the better-documented scientific studies, including human studies, point toward a value of 10000, it was agreed that a somewhat larger value could be justified. It was also agreed that, for battlefield purposes, inhalation was a more critical entry route than percutaneous for Army and Air Force personnel. A Navy representative, however, noted that penetration of ship spaces with chemical agents where personnel were masked but not suited could lead to a condition where percutaneous exposure was dominant.
(8) Reutter-Wade did not provide an estimate for this toxicity value, although several other sources appeared to be consistent.
(9) The workshop recommended a value of 1.0 with the caveat that more research was needed. Moreover, the probit slope of 5 is not based on data, but can be used as an interim value. This includes ocular exposure.
(10) The LCt50 value was increased slightly from the Reutter-Wade value, both to indicate lack of precision in the estimate (there are no human data) and to be consistent with the increase in the LCt50 for GB.
(11) Few data are available; this ECt value was based on the assumption that GD is four times as toxic as GB.
(12) The LCt50 value applies to unclothed individuals and null wind conditions. Different clothing conditions and wind speeds would produce different numbers.
(13) Threshold effects are defined as the midpoint of a dosage range at which effects begin to occur in the sample population.
(14) This curve should only be used when not superceded by a more severe condition.
(15) Observed mortality rates from HD in World War I, together with reports written in the 1940s and data from non-human primate studies, suggest the value for HD percutaneous vapor proposed by Reutter-Wade may be too low. The Reutter-Wade value is based on a review of animal studies that calculated mortality based on vesication, to which humans are the most vulnerable species. That study discounted data from non-human primate studies, since non-human primates are highly resistive to vesication. However, the mechanism of mortality from HD percutaneous vapor is currently unknown. Some data suggest that mortality may not result from vesication but from immune suppression and other effects similar to those caused by radiation. Non-human primates provide a very good model for radiation injuries in humans; if HD is in fact radiomimetic, greater weight should be given to data from non-human primate studies suggesting a higher value. This would be more consistent with experience in battlefield use of HD, as well. For these reasons, the workshop agreed that a higher median value was warranted.
(16) Animal studies tend to support the value of 900 provided by Reutter-Wade, whereas historical evidence appears to support a higher value. The workshop agreed that 1000 was a defendable number.
(17) This condition assumed masked soldiers with eye protection.
(18) For HD, severe effects consist of vesication.
(19) This effect category was renamed ocular vapor since the effects are specific to the eye and are not systemic. Moderate temperatures are assumed.
(20) The Reutter-Wade median was rounded to 600 to avoid false precision, as suggested by the NRC. The probit slope was increased to 3 to be consistent with other non-lethal effects.

3. Guidelines for Use

As with all human toxicity estimates, the recommended estimates are valid only for the given exposure conditions. All human toxicity estimates have inherent confidence limits around them. These confidence limits are a function of the dose-response curve and the underlying data upon which the estimates are based. Because of the extrapolation necessary (from animals to humans and/or from less-than-optimal toxicological data) in formulating the estimates, the confidence limits cannot be well defined. Users will encounter situations that include conditions that vary from the given exposure conditions for the estimates in this report. Often, this will require further review of references and/or coordination with others to develop solutions to these problems. In these cases, the estimates in this report will serve as a solid basis for departure and further extrapolation. In all cases, it is important to thoroughly document references and methodologies that are used.

There are key differences between the nature of the effects of nerve and mustard agents. The medical effects of nerve agent exposure by any route are attributable to inhibition of the enzyme acetylcholinesterase (either locally or systemically); the signs and symptoms observed will depend on factors such as route of exposure and dosage.

In contrast, the medical effects of sulfur mustard (HD) exposure differ by the route of exposure because significantly different mechanisms of injury are involved:

- Lethality by inhalation of HD vapor at high concentrations occurs by an unknown mechanism.
- Lethality by percutaneous exposure to liquid mustard (and presumably high concentrations of percutaneous vapor) is due to immunosuppression of the bone marrow and peripheral white blood cells/lymphocytes. Death is usually attributed to overwhelming systemic infection.
- Non-lethal exposures to percutaneous vapor result in "classic" vesication (blistering) of the exposed skin surface due to specific effects at the dermal-epidermal junction (the impact of secondary bacterial infections is not considered).
- Ocular vapor exposures result in direct irritation to the eye (which doesn't actually blister).

As noted previously, values for vapor inhalation apply to two-minute dosages. It is common practice to invoke Haber's law and assume that these values apply for exposures of different durations. But this is not true for G-agents. The panel observed

that the value for 10-minute exposure is 1.67 times that of a 2-minute exposure. The inhalation values for the G-agents can probably be extrapolated from 2 minutes through 60 minutes with reasonable confidence. The accuracy of extrapolating below 2 minutes and beyond 60 minutes is unknown. Methods of performing these extrapolations were not addressed or agreed upon at this meeting. As a general rule, the greater the extrapolation from the original data, the greater the resulting uncertainty.

Mustard agents appear to become more toxic as exposure time increases, because there are no detoxification or homeostatic compensatory mechanisms. The exact relationship between Ct and exposure time is not known.

Also as noted, percutaneous vapor values are for 30-minute exposures. The accuracy of extrapolations beyond two hours is unknown.

Probit slopes allow casualties to be calculated at lower and higher values than the medians, using standard methods. Extrapolations below the 16th percentile and above the 84th have low reliability.

Percutaneous vapor values are for unclothed individuals. There are no agreed-upon conversion factors for clothed individuals.

As noted earlier, all the inhalation values in the tables are appropriate for minute volumes of 15 liters per minute. Some participants at the workshop observed that inhaled dosages are roughly linearly proportional to the minute volume, up to volumes of 50 liters. Hence, if the minute volume is doubled to 30 liters, the inhaled amount is also doubled and the LCt50 is halved. However, it was also noted that at least one source[2] reported that for GB, an increase in minute volume by a factor of 4 resulted in a Ct value that was 36 percent of the original value.

These values all apply to 70 kg male soldiers. These agents will be of different toxicity to female soldiers, because of weight differences and gender differences, and will be more toxic to the general population. Factors of 2 and 10 for the general population or sensitive subgroups were mentioned at the workshop, but there was no consensus on these values.

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[1] Franke, Major Siegfried, *Textbook of Military Chemistry*, Military Publisher of the German Democratic Republic, Berlin, 1977.

C. RECOMMENDATIONS FOR FUTURE EFFORTS

It is clear from the notes to the tables and from the above discussion that, in spite of decades of research, there is still considerable uncertainty about the effects of chemical agents, particularly when extrapolated from central estimates. It is also clear that the primary data supporting much of the earlier work are no longer available. Thus, a major recommendation of the workshop is to prepare a permanent archive of data relevant to the estimation of chemical agent toxicity. Much information was collected in the process of preparing the Reutter-Wade report that could provide the core of such an archive. It may be impossible to repeat many of these experiments, so ensuring the long-term availability of this information will be a valuable service. Reproducing this archive in DTIC would ensure widespread availability to future researchers.

Additional efforts are required to address situations not covered by these estimates. These include:

- Longer exposures and lower concentrations,
- The effect of clothing,
- Mixed populations (male and female soldiers, civilians).

In some cases, laboratory research is needed, while in others, such as with civilians, laboratory research is infeasible and community agreement on appropriate adjustment factors is needed.

There is also a requirement to address the methodology used by analysts to employ these values in risk assessments. Probit-based methodologies may not be suitable for all cases, particularly when effects are different for different routes of entry or when effects may result from more than one route of entry, such as for HD. Toxic load and other candidate methodologies should be explored to determine if they provide better estimates of agent effects. However, studies to generate additional data may be needed to test alternative methodologies.

Some members of the workshop felt that there was a need for an analysts' handbook, fully describing the ranges in which the existing estimates are valid, and providing rules of thumb for adjustments when those ranges are exceeded. Example standard calculations and full references to the aforementioned data archives would also be provided.

The workshop did not reach a consensus on which additional agents or on which different forms of agents (such as dusty agents) needed to be addressed next with regard to establishing agreed toxicity values. This prioritization needs to originate in the policy community rather than in the research community.

Finally, there was concern expressed regarding the validity of past work, if it was based on values different from those agreed upon at this workshop. Each situation must be viewed separately. In some cases, parameter changes may make little difference in the results. There were presentations made at the workshop that suggested that changes in probit slope values may not produce large differences in the results of some analyses. In other cases, it may be that only relative, rather than absolute, results are important, and changes in toxicity values may not change the relative rankings of outcomes. In yet other cases, programmatic decisions may have already been made that would be difficult or expensive to revisit. For new work especially, however, these values should be used unless there are significant and well-documented reasons for deviating. These values are the best estimates we have for these six agents, and they represent the consensus of representatives of the scientific, medical, analytical, and operational communities based on extensive examination of available data and careful review of that examination.

REFERENCES

[1] Reutter, Sharon A. and Wade, John V., LTC., Edgewood Research, Development and Engineering Center, "Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier, (U)" ERDEC-SP-018, March 1994. (SECRET)

[2] Army Science Board, "Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier," April 1995.

[3] National Research Council Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, *Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents*, National Academy Press, Washington, D.C., 1997.

OTHER REFERENCES OF INTEREST

[4] Life Systems, Inc., "Information for Combat Developers on Performance Effects from Exposure to Mustard Agent," submitted to U.S. Army Center for Health Promotion and Preventive Medicine, TR-1605-6C, December 16, 1997.

[5] Life Systems, Inc., "Information for Combat Developers on Performance Degrading Effects from Exposure to G-Nerve Agents," submitted to U.S. Army Center for Health Promotion and Preventive Medicine, TR-1605-10B, December 16, 1997.

[6] Life Systems, Inc., "Information for Combat Developers on Performance Degrading Effects from Exposure to VX," submitted to U.S. Army Center for Health Promotion and Preventive Medicine, TR-1605-11B, December 16, 1997.

[7] Memorandum, Walter W. Hollis to General William W. Crouch, "Guidelines for Application of Toxicity Estimates," November 3, 1997.

[8] Memorandum, Stephen L. Kistner to Director, Ballistics Missile Defense Organization, "Toxicity Values for Use in the Post-Engagement Ground Effects Model," November 12, 1997.

[9] Memorandum, Col. Patricia L. Nilo to the Joint Service Integration Group and the Joint Service Material Group, "Membership on Integration Product Team—Application of Chemical Agent Toxicity Estimates," December 23, 1997.

[10] Memorandum, Stephen L. Kistner to Commander, U.S. Army Edgewood Research, Development and Engineering Center, "Clarification of Rationale for Toxicity Values," March 9, 1998.

[11] Memorandum, Col. Robert E. Hilliard to Deputy Commander, U.S. Army Space and Missile Defense Command, Missile and Space Technology Center, "Summary of Toxicity Values for the Post Engagement Ground Effects Model," March 19, 1998.

APPENDIX A: MEMORANDUM FOR THE RECORD

IDA

Strategy, **F**orces and
Resources **D**ivision

Jeffrey H. Grotte, Deputy Director

Memorandum

TO	The Record	DATE	25 May 2001
FROM	J. H. Grotte		
SUBJECT	Regarding GB Toxicity Estimates Presented in the Toxicity IPT Workshop		

Background

The report of the Toxicity IPT Workshop held at the Institute for Defense Analyses during May, 1998, has not been released. Although all participants left the workshop agreeing that the values for agent toxicity that had been developed during the workshop were a suitable set of *interim* values for the modeling of chemical agent effects from a defensive standpoint, subsequent objections were raised. The objection of continuing concern is the proposed value for the GB two-minute inhalation LCT_{50}. The Workshop adopted the value published in the Reutter-Wade (RW) report[3]. This value is 35 mg-min/m^3, half of the previously-accepted value of 70 mg-min/m^3 published in FM 3-9. Toxicity values for other G agents are based on this value, hence concerns for this value translate into concerns for other values.

The RW value for inhalation LCT_{50} for a two-minute exposure to GB was derived from a table of values on page 231 of the RW report, which gives ten-minute LCT_{50}s for several animal species. RW estimates the human LCT_{50} by fitting a power function (linear in terms of logarithms of both dependent and independent variables) relating ten-minute LCT_{50} to the independent variable MV/WT (minute volume divided by mass). The value for man is determined by evaluating the fit function at MV/WT equal to 0.214, and multiplying the result by 0.6 to obtain the two-minute LCT_{50}[4].

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[3] Reutter, Sharon A. and Wade, John V., LTC, Edgewood Research, Development and Engineering Center, *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier*, ERDEC-PS-018, March 1994. (SECRET)

[4] Multiplying by 0.6 is a statement that Haber's Law, which says that effective dosage is independent of exposure time, does not hold for GB.

Based on archival human data, the Committee on Toxicology of the National Research Council (NRC) recommended that the RW value be further lowered to some unspecified value, to be determined by future research. Pending such research, the Workshop accepted the RW estimated human GB LCT_{50} as an acceptable interim value.

Two objections have been raised to this value. The first concern was that reproducing the regression resulted in a different value (two-minute LCT_{50} = 45). Further discussions with Dr. Reutter revealed this discrepancy to be due to the fact that the RW methodology rounded the MV/WT values to one decimal place before performing the fit, but did not note this step in the report.

The second objection was that the mass and minute volume for the pig provided in the source data table were significantly different from the pig used in the LCT_{50} determination. To be sure, the RW report cautions that "values given for weight and respiratory parameters do not necessarily apply to the experimental population for which the LCT_{50} was determined" for any of the species, but the appropriate pig values were: mass equal to 7.5 kg and minute volume equal to 3.53 l/min, according to the source material [Silver[5]].

Discussion

One can argue whether rounding before performing the regression was methodologically optimal. The rationale for doing so was that three-decimal place precision was unwarranted given natural species variation and the caveat noted above that the independent variables were not specific to the experimental populations used. The difference between the two-minute human values (45 for the unrounded case, 37 for the rounded case) is small given the uncertainties in the population characteristics and the LCT_{50} determinations.

The pig values are somewhat more difficult to resolve. The table below gives two-minute human LCT_{50} values for a variety of "corrections" based on regressions performed at IDA.

Correction	***Resulting 2-minute human LCT_{50}***
Omitting pig data	55 mg-min/m3
Omitting pig data and rounding	46 mg-min/m3
Substituting small pig	50 mg-min/m^3
Substituting small pig and rounding	46 mg-min/m^3

[5] Silver, S. D, *The Estimation of the Toxicity of GB to Man*, MLRR 23, Chemical Corps Medical Laboratories Research Report, Army Chemical Center, MD, June 1953, declassified report.

Given these results, it is possible to speculate that if the appropriate pig data had been used, or if the pig data had not been included, or if the regressions were performed prior to rounding, RW might have produced a different estimate for human two-minute LCT_{50}. However, given that: 1) the differences between the RW value of 35 mg-min/m^3 and the values in the above table are relatively small (considering the uncertainties inherent in estimating toxicity), 2) the RW value is more conservative from a defensive perspective than any of the revised values, 3) the NRC has cited human data indicating a potentially lower value[6], and 4) recent analyses[7] performed at the Edgewood Chemical Biological Center on the data cited in Silver produce a two-minute LCT_{50} value of 29 mg-min/m^3, the RW value appears to be a reasonable estimate.

Hence, we feel that there is little to be gained at this point by altering this estimate, which is likely to change as more research is conducted, and considerable value in releasing the Toxicity IPT Workshop Report.

It is important to remember that a number of recommendations made by the Workshop *differ* from the RW values. Small changes were made in values for the percutaneous vapor LCT_{50} for G-agents, in the ED_{50} (severe effects) value for VX percutaneous liquid, and in the LCT_{50} value for HD inhalation vapor. Probit slope values were rounded to the nearest integer values for all agents. A significant change was made for the HD percutaneous vapor LCT_{50} value, where the Workshop recommended using the higher value contained in FM 3-9 rather than the RW value. Further, the Workshop recommended values for the percutaneous vapor ECT_{50} (severe effects) for G-agents, and provided estimates for probit slopes not presented in RW.

The purpose of the Workshop was to provide the defense community a consistent set of values that could be used by analysts addressing chemical agent issues. In the absence of the Workshop report, analysts are constrained to use the official FM 3-9 values (which do not include probit slopes at all), although there is growing consensus that these are not sufficiently conservative, or the unofficial RW values, which some analysts are already using in their studies. The Workshop values provide a more complete set of estimates that have been reviewed and adjusted by the Workshop participants, who represented "the chemical defense community, the medical community, the analytical community, three services, the Joint Service Integration Group, and the

---

[6] These data are presented for GB in Table 16 on page 92 of the Reutter-Wade report. In addition, on page 232 and elsewhere, RW refers to an unpublished report by James. Although the language on page 232 appears to indicate that the James report justifies only the RW regression methodology, a private communication from Dr. Reutter indicates that this report also supports the 35 value as well. IDA has not had an opportunity to review this unpublished report.

[7] A briefing and accompanying material were presented to visitors to the Edgewood Chemical Biological Center from IDA and OSD(S&TR) on May 21, 2001. The methodology used fit LCT_{50} values for a variety of animals from the Silver reference to a function using body mass and exposure times as independent variables.

Joint Service Materiel Group.[8]" Releasing this report with the interim GB LCT_{50} value would fulfill the original intent of the Workshop sponsor to provide a baseline of toxicity values that the defense community could share in a consistent manner to address critical chemical defense issues.

[8] From the Report of the Workshop.

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13. ABSTRACT (Maximum 200 words)

Although many studies and experiments have been performed over many years to establish the toxicity of chemical weapons agents, estimates of lethal and effective dosages vary considerably. A recent study by the US Army reviewed all available past data and recommended a set of lethality values. This study was reviewed by the National Research Council, which proposed changes to some of the recommendations of the Army study. Because a consistent, agreed-upon set of toxicity values is vital to the development of chemical defensive measures, the US Army Office of the Deputy Chief of Staff for Operations sponsored a workshop at the Institute for Defense Analyses that brought together key representatives of the chemical defense community to reach a consensus on interim toxicity values for the agents GA, GB, GD, GF, VX, and HD. The results of this workshop are summarized in this document.

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* Note: The following is the unclassified Table 1 from the Reutter-Wade, 1994 classified report that served as the initial basis for the follow-on analyses resulting in the interim-certified military acute toxicity estimates that are documented in the IDA report (Grotte and Yang, 2001)

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Table 1. Summary of Existing and Recommended Estimates (U)

	GA		GB		GD		GF		VX		HD	
	Existing*	Recom-mended	Existing*	Recom-mended	Existing*	Recom-mended	Existing*	Recom-mended	Existing*	Recom-mended	Existing*	Recom-mended
Percutaneous Vapor 30–50 minute exposure; all units = mg min/m³												
	lethal mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.	
LCt_{50}	20,000	15,000	15,000	10,000		2500	15,000	2500		150	10,000	5000
Slope		4.8		(4.8)		(5.5)		3.7		(5.5)		(6.9)
Conf.		Y–		Y–		R+		R±		R±		Y±
	severe mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.	
ECt_{50}										25	2000	500
Slope										(5.5)		(2.2)
Conf.										Y±		G–
	severe hot temp.		**severe** hot temp.		**severe** hot temp.		**severe** hot temp.		**severe** hot temp.		**severe** hot temp.	
ECt_{50}											1000	<200
Slope												
Conf.												G–
	threshold mod. temp.		**threshold** mod. temp.		**threshold** mod. temp.		**threshold** mod. temp.		**threshold** mod. temp.		**threshold** mod. temp.	
ECt_{50}		2000		1200		300		300		10		50
Slope												
Conf.		G–		G–		R±		R±		Y–		G–
	threshold hot temp.		**threshold** hot temp.		**threshold** hot temp.		**threshold** hot temp.		**threshold** hot temp.		**threshold** hot temp.	
ECt_{50}												25
Slope												
Conf.												G–
Vapor Inhalation 2–10 minute exposure; 15 liter minute volume: all units = mg min/m³												
	lethal mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.	
LCt_{50}	135	70	70	35	70	35		35	30	15	1500	900
Slope		12.0		12.0		12.0		12.0		6.3		5.7
Conf.		Y±		Y±		Y–		Y–		R±		Y–
	severe mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.	
ECt_{50}		50	35	25	35	25		25	25	10	200	100
Slope		10.0		10.0		10.0		10.0		5.9		
Conf.		Y±		Y±		Y–		Y–		R±		G–
Ocular or Nasal Vapor (Mild Effects) 2–10 minute exposure; independant of minute volume: all units = mg min/m³												
ECt_{50}	0.9	0.5	2	0.5		0.2		0.2	0.09	0.09	>50	25
Slope												
Conf.		Y+		G±		R±		R±		Y±		G–
Percutaneous Liquid all units = mg/70 kg man												
	lethal mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.		**lethal** mod. temp.	
LD_{50}	1500	1500	1700	1700	350	350		350	10	5	7000	1400
Slope		4.8		4.8		5.5		3.9		5.5		6.9
Conf.		Y–		Y–		Y–		R±		R±		Y–
	severe mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.		**severe** mod. temp.	
ED_{50}		880		1000		200		200	5	2.5		610
Slope		(4.8)		(4.8)		(5.5)		(3.9)		5.5		2.2
Conf.		R±		R±		R±		R±		R±		Y±

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(U) **Key: * Existing** = single most widely quoted estimate. **Conf.** = confidence level of estimate. **R** (red) indicates little, if any, animal data and no human data for defined endpoint by specified exposure route. **Y** (yellow) = indicates little, if any, human data and insufficient animal data for specified exposure route. **G** (green) = indicates appropriate human data for specified exposure route or some human data and sufficient animal data for specified exposure route and endpoint. Plus signs (+) indicate that subjective degree of confidence is higher than indicated by color code; minus signs (–) indicate converse. Parentheses ( ) indicate that slope used to calculate effects levels other than 50% was not directly obtained from data for the specified exposure route. Dark shading indicates no commonly quoted existing estimate or no recommended estimate. ECt_{50} and ED_{50} indicate ***effective*** dosages for defined level of effect. **mod. temp.** = moderate temperatures (65 - 75˚ F); **hot temp.** = hot temperatures (> 85˚ F).

Source: ERDEC-SP-018, March 1994

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APPENDIX C
OPERATIONAL RISK MANAGEMENT DEFINITIONS

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C.1 Risk Assessment Matrix

The risk assessment matrix (see Table C-1) combines severity and probability estimates to form a risk assessment for each threat. Use the matrix in Table C-1 to evaluate the acceptability of a risk and the level at which the decision on acceptability will be made. The matrix may also be used to prioritize resources, to resolve risks, or to standardize threat notification or response actions. Severity, probability, and risk assessment should be recorded to serve as a record of the analysis for future use.

Table C-1. Risk Assessment Matrix

		Probability				
Severity		**Frequent**	**Likely**	**Occasional**	**Seldom**	**Unlikely**
Catastrophic		**E**	**E**	**H**	**H**	**M**
Critical		**E**	**H**	**H**	**M**	**L**
Marginal		**H**	**M**	**M**	**L**	**L**
Negligible		**M**	**L**	**L**	**L**	**L**

References: FM 3-100.12 and FM 100-14.

E - Extremely High Risk: Loss of ability to accomplish the mission if threats occur during mission.

H – High Risk: Significant degradation of mission capabilities in terms of the required mission standard, inability to accomplish all parts of the mission, or inability to complete the mission to standard if threats occur during the mission.

M – Moderate Risk: Expected degraded mission capabilities in terms of the required mission standard will have a reduced capability if threats occur during mission.

L – Low Risk: Expected losses have little or no impact on accomplishing the mission.

C.2 Severity Categories. The following table outlines severity categories:

Table C-2. Hazard Severity Categories	
Category	**Definition**
CATASTROPHIC (I)	Loss of ability to accomplish the mission or mission failure. Death or permanent disability. Loss of major or mission-critical system or equipment. Major property (facility) damage. Severe environmental damage. Mission-critical security failure. Unacceptable collateral damage.
CRITICAL (II)	Significantly degraded mission capability, unit readiness, or personal disability. Extensive damage to equipment or systems. Significant damage to property or the environment. Security failure. Significant collateral damage.
MARGINAL (III)	Degraded mission capability or unit readiness. Minor damage to equipment or systems, property, or the environment. Injury or illness of personnel.
NEGLIGIBLE (IV)	Little or no adverse impact on mission capability. First aid or minor medical treatment. Slight equipment or system damage, but fully functional and serviceable. Little or no property or environmental damage.

C.3 Probability Categories. The following table outlines probability categories for the risk assessment matrix:

Table C-3. Probability Definitions	
Element Exposed	**Definition**
FREQUENT (A) Occurs very often, continuously experienced	
Individual Occurs very often.	Expected to occur several times during mission or operation.
All personnel exposed.	Occurs continuously during a specific mission or operation.
LIKELY (B) Occurs several times	
Individual	Occurs several times. Expected to occur during a specific mission or operation.
All personnel exposed	Occurs at a high rate but experienced intermittently.
OCCASIONAL (C) Occurs sporadically	
Individual	Occurs over a period of time. May occur during a specific mission or operation, but not often.
All personnel exposed	Occurs sporadically (irregularly, sparsely, or sometimes).
SELDOM (D) Remotely possible; could occur at some time	
Individual	Occurs as isolated incident. Remotely possible, but not expected to occur during a specific mission or operation.
All personnel exposed	Occurs rarely within exposed population as isolated incidents.
UNLIKELY (E) Can assume will not occur, but not impossible	
Individual	Occurrence not impossible, but may assume will not occur during a specific mission or operation.
All personnel exposed	Occurs very rarely, but not impossible.

APPENDIX D
SUMMARY OF CURRENT CHEMICAL WARFARE AGENT DETECTION DEVICES AND DETECTION SPECIFICATIONS

This appendix provides summary information relating to existing detection capabilities which can be compared to the types of recommended detection objectives described in this report (as introduced in Chapter 2 and then recommended in Chapter 5, Table 5-5 and Table 5-6). Figure D-1 depicts a specific example of this comparison.

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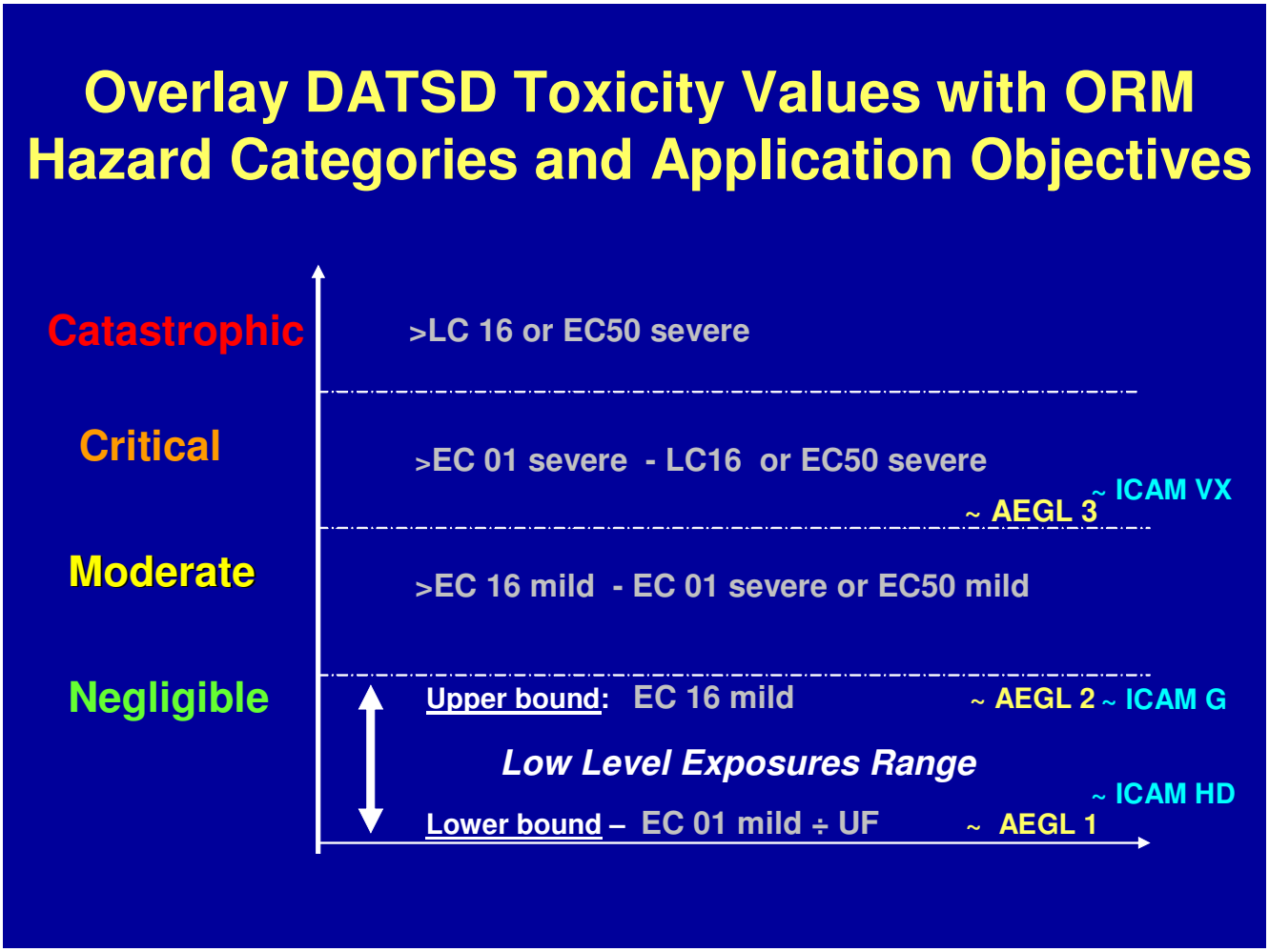
Figure D-1. Overlay DATSD Toxicity Values with Operational Risk Management Hazard Categories and Application Objectives



This figure demonstrates the current detection capabilities of the Improved Chemical Agent Monitor relating to the toxicity levels and recommended hazard severity categories described in this report (see Tables 5-1 through 5-6). See Glossary for acronym definitions.

Table D-1. Sensitivity and Limitations of Chemical Monitoring Equipment

(References: NRC, 1999, Table 4-1; USACHPPM, 2002; and Rostker, 1999)

Equipment	Phase	Agent Symbol	Sensitivity	Time	NOTES
Miniature Chemical Agent Detector (ICAD)	Vapor	G HD C AC, CK CG	0.2-0.5 mg/m^3 10.0 mg/m^3 10.0 mg/m^3 50.0 mg/m^3 25.0 mg/m^3	2min 30 sec for high levels 2min 15 sec	8 oz, pocket mounted, 4 months service, no maintenance, minimal training, audio and visual alarm, no radioactivity.
M90 D1A Chemical Agent Detector	Vapor only	G V Mustard Lewisite	0.02 mg/m^3 0.02 mg/m^3 0.2 mg/m^3 0.8 mg/m^3	10 sec 10 sec 10 sec 80 sec	15 lb w battery, radioactive source (no lics) minimal training, Ion mobility spectroscopy and metal conductivity, alarm only.
M8A1 Alarm Automatic Chemical Agent Alarm	Vapor only	GA GB GD VX HD	0.2 mg/m^3 0.2 mg/m^3 0.2 mg/m^3 0.4 mg/m^3 10.0 mg/m^3	$\leq$2 min $\leq$2 min $\leq$2 min $\leq$2 min $\leq$2 min	Vehicle battery operated, maintenance required, radioactive source (lisc required) automatic unattended operation; remote replacement.
MM-1 Mobile Mass Spectrometry Gas Chromatograph	Vapor	20-30 CWA	<10.0 mg/m^3 of surface area	$\leq$ 45 sec	Heater volatilizes surface contamination; on FOX Recon vehicle.
M-21 Remote Sensing Chemical Agent Automatic Alarm (RSCAAL)	Vapor	G H L	90.0 mg/m^3 2300 mg/m^3 500 mg/m^3	---	Line-of-sight dependent, 10-yr shelf life; 2 person portable tripod; 3 mi, passive infrared; visual audible warn from 400m.
SAW Mini-CAD	Vapor	GB GD HD	1.0 mg/m^3 0.12 mg/m^3 0.6 mg/m^3	1 min 1 min 1 min	Minimal training for field use, 1 lb, no calibration, alarm only, false alarms from gasoline vapor, glass cleaner.
Automatic Chemical Agent Alarm (ACADA) (XM22)	Vapor	G HD	0.1 mg/m^3 2.0mg/m^3	30 sec 30 sec	Vehicle mounted, battery power, radio active source (license); minimal training; audible alarm bar graph display: low, high, v. high.
Field Mini-Chemical Agent Monitor (CAM)		G V H L	<0.0001 mg/m^3 <0.0001 mg/m^3 <0.003 mg/m^3 <0.003 mg/m^3	<5 min <5 min <5 min <5 min	Designed for field industry monitoring, 10 lbs; 8 hrs training, 24/7 operations; plug-in modules increase versatility; lowest threshold.
Viking Spectratrak Gas Chromatography/Mass Spectrometry		G V HD	<0.0001 mg/m^3 <0.0001 mg/m^3 <0.003 mg/m^3	<10 min <10 min <10 min	Field use but 85 lbs; needs 120v AC, helium, 40 hrs training; lab quality y analysis; library of 62K chemicals.
HP 6890 Gas Chromatography with flame photometric detector		G V HD	<0.0001 mg/m^3 <0.0001 mg/m^3 <0.0006 mg/m^3	<10 min <10 min <10 min	Not designed for field use; gas, air, 220v AC; 40 hrs training; state-of –the art chromatography.

[a] per Rostker, 1999 Table 2-3: μ refers to micron (10^{-6}m), in reference to the minimum diameter of droplets that will cause a color change in dye-impregnated M8/M9 paper. 100µ considered equivalent to 0.02 milliliter volume.

Table D-1. Sensitivity and Limitations of Chemical Monitoring Equipment (continued)

(References: NRC, 1999, Table 4-1; USACHPPM, 2002; and Rostker, 1999)

Equipment	Phase	Agent Symbol	Sensitivity	Time	NOTES
Miniature Chemical Agent Detector (ICAD)	Vapor	G HD C AC, CK CG	0.2-0.5 mg/m^3 10.0 mg/m^3 10.0 mg/m^3 50.0 mg/m^3 25.0 mg/m^3	2min 30 sec for high levels 2min 15sec	8 oz, pocket mounted, 4 months service, no maintenance , minimal training, audio and visual alarm, no radioactivity.
M90 D1A Chemical Agent Detector	Vapor only	G V Mustard Lewisite	0.02 mg/m^3 0.02 mg/m^3 0.2 mg/m^3 0.8 mg/m^3	10 sec 10 sec 10 sec 80 sec	15lb w battery, radioactive source (no lics) minimal training, Ion mobility spectroscopy and metal conductivity, alarm only.
M8A1 Alarm Automatic Chemical Agent Alarm	Vapor only	GA GB GD VX HD	0.2 mg/m^3 0.2 mg/m^3 0.2 mg/m^3 0.4 mg/m^3 10.0 mg/m^3	$\leq$2 min $\leq$2 min $\leq$2 min $\leq$2 min $\leq$2 min	Vehicle battery operated, maintenance required, radioactive source (lisc required) automatic unattended operation; remote replacement.
MM-1 Mobile Mass Spectrometry Gas Chromatograph	Vapor	20-30 CWA	<10.0 mg/m^3 of surface area	$\leq$ 45 sec	Heater volatilizes surface contamination; on FOX Recon vehicle.
M-21 Remote Sensing Chemical Agent Automatic Alarm (RSCAAL)	Vapor	G H L	90.0 mg/m^3 2300 mg/m^3 500 mg/m^3	---	Line-of-sight dependent, 10-yr shelf life; 2 person portable tripod; 3 mi, passive infrared; visual audible warn from 400m.
SAW Mini-CAD	Vapor	GB GD HD	1.0 mg/m^3 0.12 mg/m^3 0.6 mg/m^3	1 min 1 min 1 min	Minimal training for field use, 1 lb, no calibration, alarm only, false alarms from gasoline vapor, glass cleaner.
Automatic Chemical Agent Alarm (ACADA) (XM22)	Vapor	G HD	0.1 mg/m^3 2.0mg/m^3	30 sec 30 sec	Vehicle mounted, battery power, radio active source (license); minimal training; audible alarm bar graph display: low, high, v. high.
Field Mini-Chemical Agent Monitor (CAM)		G V H L	<0.0001 mg/m^3 <0.0001 mg/m^3 <0.003 mg/m^3 <0.003 mg/m^3	<5 min <5 min <5 min <5 min	Designed for field industry monitoring, 10 lbs; 8 hrs training, 24/7 operations; plug-in modules increase versatility; lowest threshold.
Viking Spectratrak Gas Chromatography/ Mass Spectrometry		G V HD	<0.0001 mg/m^3 <0.0001 mg/m^3 <0.003 mg/m^3	<10 min <10 min <10 min	Field use but 85 lbs; needs 120v AC, helium, 40 hrs training; lab quality y analysis; library of 62K chemicals.
HP 6890 Gas Chromatography with flame photometric detector		G V HD	<0.0001 mg/m^3 <0.0001 mg/m^3 <0.0006 mg/m^3	<10 min <10 min <10 min	Not designed for field use; gas, air, 220v AC; 40 hrs training; state-of –the art chromatography.

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APPENDIX E
CHEMICAL WARFARE TOXICITY ASSESSMENT AND EXTRAPOLATION SUPPORTING INFORMATION AND TABLES

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E.1 Description of Cumulative Exposure (Log-Probit) Analysis

In the current analysis, standard statistical methods have been employed to extrapolate from these median (50^{th} percentile) IDA toxicity for ECt (threshold), estimates to other percentile levels. **Statistically, values below the 16^{th} and above the 84^{th} percentiles (single standard deviation) have low reliability**. However, the values at the lower end of the log-normal distribution curve are particularly critical for estimating minimum effects levels within the Negligible hazard range while higher percentiles are useful for presenting more detailed information about more significant health impacts. Therefore, the 1^{st} and 16^{th} percentiles, as well as the 84^{th} and 99^{th}, have been calculated for G-series nerve agents, nerve agent VX, and the vesicant agent HD.

These calculations were performed using the following assumptions concerning the ECt_{50} and the probit slope—

- That for any specific concentration value, there was a corresponding random variable for percent affected containing a probability distribution with a finite mean and variance.

- That all of the determined percent affected were statistically independent from each other.

- That the average value for percent affected is a straight-line function of concentration.

- That the variances for concentration and percent affected were statistically equal.

- That for any fixed value for concentration, there was a normal distribution for percent affected.

- That the intercept used in the calculation was equivalent to the difference between the calculated 50 percent response and that provided in the IDA report.

The following limitations also apply to the calculated results:

- The probit distribution was derived from a common error function derived from 50 percent adjusted to a slope of 5.0.

- A normally distributed population is assumed with the results sensitive to outlying points.

- Most importantly, the frequency distribution of each point along the line becomes more asymptotic as it approaches the extremes of the range. That is to say that in the probit range of 16 percent to 84 percent (those values associated with 1 standard deviation (SD)) the error in the line changes gradually. Beyond this range, the error changes ever more rapidly (Kleinbaum, et. al., 1988). As a consequence, the confidence limit in a 1 percent value is broad. Statistically, the most confidence in the results would be for the interval between 16 percent and 84 percent.

E.2 Time Scaling and the ten-Berge Method

The NRC/COT (2001) method for time extrapolations is based on a study conducted by ten Berge, et al. (1986) in which an assessment of LC_{50} data indicated that there existed a chemical-specific relationship between exposure concentration and exposure duration that was often exponential. This relationship is expressed by the equation $C^n \times t = k$ where n represents a chemical-specific and even toxic endpoint-specific, exponent (NRC/COT 2001). This relationship is basically in the form of a linear regression analysis of the log transformation of the plot of C vs. t. The empirically derived n in the ten Berg, et. al., (1986) study ranged from 0.8 to 3.5. Haber's Law is a special case where $n = 1$.

The NRC/COT (2001) approach is to use, when available, chemical-specific toxicity and exposure data to derive a chemical-specific and health effect-specific exponent (n value) for use in extrapolating to exposure durations not included in the experimental data. From the data of ten Berge et. al., NRC/COT decided to use an n of 1 as an estimate of the lower boundary and an n of 3 an estimate of the upper boundary of the range of n values. Therefore, in the absence of adequate toxicity and exposure data NRC/COT (2001) uses as a default value an n of 1 to extrapolate from shorter to longer exposure durations and an n of 3 to extrapolate from longer to shorter exposure durations. These values may be modified depending on the available supporting data, and on the scientific reasonableness of the selections.

Table E-1. Distribution of Mustard Gas Injuries on Bodies of World War I Casualties[a]

Body Part	Reported injuries, %
Eyes	86.1
Respiratory tract	75.3
Scrotum	42.1
Face	26.6
Anus	23.9
Back	12.9
Armpits	12.5
Neck	12.0
Arms	11.7
Chest	11.5
Legs	11.4
Buttocks	9.8
Abdomen	6.4
Thighs	6.0
Hands	4.3
Feet	1.5

[a] Percentage of mustard gas injuries to various body parts in 6980 World War I casualties (Gilchrist, 1928; Blewett, 1986).

Table E-2. Estimated Relative Rank in Susceptibility of Body Regions to Operationally Adverse Concentrations of Chemical Warfare Agents (derived from Table 2-3; NRC/BAST, 1997) [a,b]

Body Region	VX [b]	HD
Scrotum	1.0	1.0
Chin and neck	3.2	3.3
Ears	4.1	4.2
Cheeks and neck	4.3	4.4
Nape (back of neck)	15.4	15.7
Scalp (top of head)	6.8	6.9
Abdomen	19.9	20.4
Back	23.7	24.3
Arms (lower, volar)	25.0	25.6
Arms (upper, dorsum)	58.6	60.2
Legs (plantar, lower)	25.0	25.6
Legs (plantar, upper)	38.1	39.0
Legs (dorsum, lower)	58.6	60.2
Legs (dorsum, upper)	58.6	60.2
Knees (front)	63.8	65.4

[a] Ranking relative to scrotal dose in μg/kg (VX; estimated to cause 70% depression in RBC-ChE) or scrotal cumulative exposure in mg-min/m^3 (HD; estimated to cause local severe burns), with value of 1 (scrotum) indicating most susceptible body region. Source: Fedele and Nelson (1996) as cited in NRC/BAST (1997).

[b] Given the state and extent of existing percutaneous toxicity data, it seems reasonable to assume that the relative ranking exhibited by nerve agent VX would be shared by the G-series agents. Agent-specific vapor concentrations considered operationally adverse would vary per individual chemical and physical properties, etc.

Table E-3. Ratio of ECt_{50} (Threshold to Severe) for Nerve Agents and Sulfur Mustard				
Agent	**Exposure Pathway**	**ECt_{50} (threshold)[a]**	**ECt_{50} (severe)[a]**	**Threshold: Severe Ratio**
GA	Inhalation vapor	1	50	0.02
	Percutaneous vapor	2000	12000	0.17
GB	Inhalation vapor	1	25	0.04
	Percutaneous vapor	1200	8000	0.15
GD	Inhalation vapor	0.4	25	0.016
	Percutaneous vapor	300	2000	0.15
GF	Inhalation vapor	0.4	25	0.016
	Percutaneous vapor	300	2000	0.15
VX	Inhalation vapor	0.1	10	0.01
	Percutaneous vapor	10	25	0.4
HD	Ocular vapor	25	100	0.25
HD (mod. temp.)	Percutaneous vapor	50	500	0.1
HD (hot temp.)	Percutaneous vapor	25	200	0.125

[a] Grotte, JH and LI Yang (2001). Values derived for male military population.

Table E-4. Probit-Extrapolated Toxicity Values[a] for Inhalation/Ocular Exposures						
Agent	**Effect Level (endpoint)**	**Ct01[b]**	**Ct16**	**Ct50**	**Ct84**	**Ct99**
GA	Lethality (LCt)	45	58	70	85	109
GA	ECt (severe)	29.3	39.8	50	62.9	85.4
GA	ECt (mild)	0.343	0.633	1.0	1.581	2.919
GB	Lethality (LCt)	22.4	28.9	35	42.4	54.7
GB	ECt (severe)	14.6	19.9	25	31.4	42.7
GB	ECt (mild)	0.343	0.633	1.0	1.581	2.919
GD	Lethality (LCt)	22.4	28.9	35	42.4	54.7
GD	ECt (severe)	14.6	19.9	25	31.4	42.7
GD	ECt (mild)	0.164	0.273	0.4	0.586	0.977
GF	Lethality (LCt)	22	29	35	42	55
GF	ECt (severe)	14.6	19.9	25	31.4	42.7
GF	ECt (mild)	0.137	0.253	0.4	0.632	1.168
VX	Lethality (LCt)	6.1	10.2	15	22	36.6
VX	ECt (severe)	4.1	6.8	10	14.6	24
VX	ECt (mild)	0.03	0.06	0.10	0.18	0.38
HD	Lethality (LCt)	410	683	1000	1465	2442
HD	ECt (severe, ocular)	16.8	47	100	215	596
HD	ECt (mild, ocular)	4.2	11.7	25	53.6	149.1

[a] Toxicity values here are "Cts" in units of mg-min/m^3, they are not time-specific. See Sections 4.5 and 4.6 for time-extrapolation methods and Tables E-5 and E-6 for duration-specific concentration (C) estimates in mg/m^3.

[b] This Table presents toxicity values developed prior to adjustments for variable susceptibility within the military population. Adjustment procedures to account for susceptibility and to estimate population thresholds are described in Sections 4.2, 4.5.2, 4.6.1, and Table 4.4. Footnotes on Tables E-5 and E-6 demonstrate examples of this adjustment.

Table E-5. Time-Extrapolated Toxicity Estimates (mg/m^3) for 10-min and 60-min Inhalation/Ocular Exposures

Agent	Endpoint	C for 1%[a]		C for 16%		C for 50%		C for 84%		C for 99%	
		10-min	60 min	10-min	60-min	10-min	60-min	10-min	60-min	10-min	60-min
GA	Lethality	10.2	4.09	12.93	5.28	15.65	6.39	18.94	7.73	24.46	9.99
GA	ECt (severe)	6.54	2.67	8.89	3.63	11.18	4.56	14.06	5.74	19.10	7.80
GA	ECt (mild)	0.077[a]	0.031[a]	0.141	0.058	0.224	0.091	0.353	0.144	0.653	0.266
GB	Lethality	5.01	2.04	6.47	2.64	7.83	3.20	9.47	3.87	12.23	4.99
GB	ECt (severe)	3.27	1.34	4.45	1.82	5.59	2.28	7.03	2.87	9.55	3.90
GB	ECt (mild)	0.077[a]	0.031[a]	0.141	0.058	0.224	0.091	0.353	0.144	0.653	0.266
GD	Lethality	5.01	2.04	6.47	2.64	7.83	3.20	9.47	3.87	12.23	4.99
GD	ECt (severe)	3.27	1.34	4.45	1.82	5.59	2.28	7.03	2.87	9.55	3.90
GD	ECt (mild)	0.037[a]	0.015[a]	0.061	0.025	0.089	0.037	0.131	0.053	0.218	0.089
GF	Lethality	5.01	2.04	6.47	2.64	7.83	3.20	9.47	3.87	12.23	4.99
GF	ECt (severe)	3.27	1.34	4.45	1.82	5.59	2.28	7.03	2.87	9.55	3.90
GF	ECt (mild)	0.031[a]	0.013[a]	0.057	0.023	0.089	0.037	0.141	0.058	0.261	0.107
VX	Lethality	1.37	0.56	2.29	0.93	3.35	1.37	4.91	2.01	8.19	3.34
VX	ECt (severe)	0.92	0.37	1.53	0.62	2.24	0.913	3.28	1.34	5.46	2.23
VX	ECt (mild)	0.006[a]	0.002[a]	0.013	0.005	0.022	0.009	0.040	0.016	0.085	0.035
HD	LCt	41	6.83	68	11.379	100	16.67	146	24.412	244	40.70
HD	ECt (severe, ocular)	1.7	0.280	5	0.777	10	1.67	21	3.576	60	9.94
HD	ECt (mild, ocular)	0.419[a]	0.070[a]	1.165	0.194	2.50	0.417	5	0.894	14.91	2.48

[a] Population threshold estimates (PTEs) can be derived by applying (dividing by) composite uncertainty factors (UFs) of "10" to nerve agent and "3" to sulfur mustard EC_{01} (mild) toxicity estimates (these UFs account for the variable susceptibly within the military population). See Sections 4.2, 4.5.2, 4.6.1, and Table 4.4 for more information.

Table E-6. Time-Extrapolated Toxicity Estimates (C in mg/m^3) for 8-hr and 24-hr Inhalation/Ocular Exposures for Each IDA Parameter

Agent	IDA Parameter	C for 1% [a]		C for 16%		C for 50%		C for 84%		C for 99%	
		8 hr	24 hr	8 hr	24 hr	8 hr	24 hr	8 hr	24 hr	8 hr	24 hr
GA	Lethality	1.45	0.48	1.87	0.62	2.26	0.75	2.73	0.91	3.53	1.18
GA	ECt (severe)	0.94	0.31	1.28	0.43	1.61	0.54	2.03	0.67	2.76	0.92
GA	ECt (mild)	0.011 [a]	0.0036 [a]	0.020	0.0067	0.032	0.011	0.051	0.017	0.094	0.031
GB	Lethality	0.72	0.24	0.93	0.31	1.13	0.38	1.37	0.46	1.77	0.59
GB	ECt (severe)	0.47	0.16	0.64	0.21	0.81	0.27	1.01	0.34	1.38	0.46
GB	ECt (mild)	0.011 [a]	0.0036 [a]	0.020	0.0067	0.032	0.011	0.051	0.017	0.094	0.031
GD	Lethality	0.72	0.24	0.93	0.31	1.13	0.38	1.37	0.45	1.77	0.59
GD	ECt (severe)	0.47	0.16	0.64	0.21	0.81	0.27	1.01	0.34	1.38	0.46
GD	ECt (mild)	0.0053 [a]	0.0018 [a]	0.009	0.003	0.013	0.0043	0.019	0.006	0.032	0.011
GF	Lethality	0.72	0.24	0.93	0.31	1.13	0.38	1.37	0.45	1.77	0.59
GF	ECt (severe)	0.47	0.16	0.64	0.21	0.81	0.27	1.01	0.34	1.38	0.46
GF	ECt (mild)	0.0044 [a]	0.0015 [a]	0.008	0.0027	0.013	0.0043	0.020	0.0067	0.038	0.013
VX	Lethality	0.20	0.067	0.33	0.11	0.48	0.16	0.71	0.24	1.18	0.39
VX	ECt (severe)	0.13	0.043	0.22	0.073	0.32	0.11	0.47	0.16	0.79	0.26
VX	ECt (mild)	0.0008 [a]	0.00027 [a]	0.0018	0.0006	0.003	0.001	0.0057	0.0019	0.012	0.004
HD	LCt	0.85	0.28	1.42	0.47	2.08	0.69	3.05	1.02	5.09	1.70
HD	ECt (severe, ocular)	0.035	0.012	0.10	0.03	0.21	0.07	0.45	0.15	1.24	0.41
HD	ECt (mild, ocular)	0.0087 [a]	0.0029 [a]	0.0243	0.0081	0.052	0.017	0.112	0.037	0.31	0.10

[a] Population threshold estimates (PTEs) can be derived by applying (dividing by) composite uncertainty factors (UFs) of "10" to nerve agent and "3" to sulfur mustard EC_{01} (mild) toxicity estimates (these UFs account for the variable susceptibly within the military population). See Sections 4.2, 4.5.2, 4.6.1, and Table 4.4 for more information.

Table E-7. *k* Values to be Used in ten-Berge Equation to Derive Agent Concentrations for Different Exposure Durations[a]

Agent	$EC_{01\ mild}$	$EC_{16\ mild}$	$EC_{50\ mild}$	$EC_{84\ mild}$	$EC_{99\ mild}$
GA	0.000987	0.00333	0.00833	0.0208	0.0710
GB	0.000987	0.00333	0.00833	0.0208	0.0710
GD	0.000224	0.000621	0.00133	0.00286	0.00795
GF	0.000156	0.000534	0.00133	0.00333	0.0114
VX	0.00000572	0.0000265	0.0000833	0.000262	0.00121
HD	0.0699	0.194	0.417	0.894	2.48

[a] ten-Berge equation $C^n t = k$; where t = exposure duration in hours; $n = 2$ for the nerve agents for exposure durations of 10 min to 8 hr; for exposure durations between 8 hr and 24 hr, a straight-line extrapolation from the 8-hr values (i.e., k = Ct for 8 hr) is recommended; $n = 1$ for HD for all exposure durations from 10 min to 24 hr.

Table E-8. Extrapolated Toxicity Values for Percutaneous Vapor Exposures (mg-min/m^3) [a] [b]

Agent	Effect level (endpoint)	Ct01	Ct16	Ct50	Ct84	Ct99
GA	Lethality (LCt)	5,138	9,488	15,000	23,713	43,788
GA	ECt (severe)	4,111	7,591	12,000	18,971	35,030
GA	ECt (mild)	685	1,265	2,000	3,162	5,838
GB	Lethality (LCt)	4,111	7,591	12,000	18,971	35,030
GB	ECt (severe)	2,741	5,060	8,000	12,647	23,353
GB	ECt (mild)	411	759	1200	1,897	3,503
GD	Lethality (LCt)	1,229	2,048	3,000	4,394	7,326
GD	ECt (severe)	819	1,365	2,000	2,929	4,884
GD	ECt (mild)	123	205	300	439	733
GF	Lethality (LCt)	1,028	1,898	3,000	4,743	8,758
GF	ECt (severe)	685	1,265	2,000	3,162	5,838
GF	ECt (mild)	103	190	300	474	876
VX	Lethality (LCt)	61	102	150	220	366
VX	ECt (severe)	10.2	17.1	25	36.6	61
VX	ECt (mild)	4.1	6.8	10	14.6	24.4
HD	Lethality (LCt)	4,652	7,210	10,000	13,870	21,495
HD	ECt (severe; mod. temp.)	84	233	500	1073	2981
HD	ECt (threshold; mod. temp.)	8.4	23	50	107	298
HD	ECt (severe; hot temp.)	34	93	200	429	1,193
HD	ECt (threshold; hot temp.)	4.2	11.7	25	53.6	149.1

[a] Toxicity values here are "Cts"in units of mg-min/m^3, they are not time-specific. See Sections 4.6.2.2 and Table 4-8 for duration-specific concentration (C) estimates in mg/m^3.

[b] This Table presents toxicity values developed prior to adjustments for variable susceptibility within the military population. Adjustment procedures to account for susceptibility and to estimate population thresholds are described in Sections 4.2, 4.6.2, and Table 4.8.

Table E-9. Extrapolated Toxicity Values for Percutaneous Liquid Exposures (mg/70-kg man)[a]

Agent	Parameter	LD_{01} or ED_{01}	LD_{16} or ED_{16}	LD_{50} or ED_{50}	LD_{84} or ED_{84}	LD_{99} or ED_{99}
GA	Lethality	514	949	1500	2371	4379
GA	ED (severe)	308	569	900	1423	2627
GB	Lethality	582	1075	1700	2688	4963
GB	ED (severe)	343	633	1000	1581	2919
GD	Lethality	1433	239	350	513	855
GD	ED (severe)	82	137	200	293	488
GF	Lethality	120	221	350	553	1022
GF	ED (severe)	69	127	200	316	584
VX	Lethality	2.0	3.4	5.0	7.3	12
VX	ED (severe)	0.8	1.4	2.0	2.9	5
HD	LD	651	1009	1400	1942	3009
HD	ED (severe)	101	280	600	1287	3578

[a] Toxicity values in this Table are derived directly from estimates provided by Grotte and Yang, 2001, which did not present mild/threshold effects. Percutaneous Liquid Threshold Toxicity Estimates have been derived in this report – see Section 4.6 and Table 4.9.

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APPENDIX F
ADDITIONAL EXISTING TOXICITY-BASED CRITERIA FOR CHEMICAL WARFARE AGENTS

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Table F-1. Summary of Army Airborne Exposure Limits for Nerve Agents and Sulfur Mustard

Standard Name	Exposure Scenario	H/HD/HT	GA (Tabun)	GB (Sarin)	GD/GF	VX
IDLH	Worker, 1-time exposure	OLD: NA	**OLD: 0.2**	**OLD: 0.2**	**OLD: 0.06**	**OLD: 0.02**
		Proposed Army: 2	**Proposed Army: 0.1**	**Proposed Army: 0.1**	**Proposed Army: 0.05**	**Proposed Army: 0.01**
		New CDC 0.7	**New CDC**: 0.1	**New CDC**: 0.1	**New CDC**: none	**New CDC**: 0.003
STEL	Worker, occasional 15-min exposure (4x ea day)	OLD: NA	OLD: NA	OLD: NA	OLD: NA	OLD: NA
		Proposed Army: 0.003	**Proposed Army: 0.0004**	**Proposed Army: 0.0004**	**Proposed Army: 0.0002**	**Proposed Army: 0.00004**
		New CDC: 0.003	**New CDC: 0.0001**	**New CDC: 0.0001**	**New CDC: none**	**NewCDC: 0.00001**
WPL	Worker, 8-hr, daily/ 30-yr. TWA	**OLD: 0.003**	**OLD: 0.0001**	**OLD: 0.0001**	**OLD: 0.00003**	**OLD: 0.00001**
		Proposed Army: 0.0004	**Proposed Army: 0.0001**	**Proposed Army: 0.0001**	**Proposed Army: 0.00003**	**Proposed Army: 0.00001**
		New CDC: 0.0004	**New CDC: 0.00003:**	**New CDC 0.00003**	**New CDC: none**	**New CDC: 0.000001:**
GPL	General population, 24-hr/daily, lifetime TWA	**OLD: 0.0001**	**OLD: 0.000003**	**OLD: 0.000003**	**OLD: 0.000001**	**OLD: 0.000003**
		Proposed Army: 0.00002	**Proposed Army: 0.000003**	**Proposed Army: 0.000003**	**Proposed Army: 0.000001**	**Proposed Army: 0.0000003**
		New CDC: 0.00002	**New CDC: 0.000001**	**New CDC 0.000001:**	**New CDC: none:**	**New CDC: 0.0000006**

OLD

DA Pamphlet 40-173, *Occupational Health Guidelines for the Evaluation and Control of Exposure to Nerve Agents GA, GB, GD, and VX*; Medical Services, **4 December 1990**; and

DA Pamphlet 40-8, *Occupational Health Guidelines for the Evaluation and Control of Exposure to Mustard Agents H, HD, and HT*; Medical Services, **August 1991**.

Federal Register, vol. 53, No. 50, pp. 8504-8507 (*nerve and sulfur mustard agents*), **15 March 1988**.

Proposed New Army

Proposed new values per DA Pamphlet 40-173, *Occupational Health Guidelines for the Evaluation and Control of Exposure to Nerve Agents GA, GB, GD, and VX*; Medical Services**, revised (draft) February 2003**; and

DA Pamphlet 40-8, *Occupational Health Guidelines for the Evaluation and Control of Exposure to Mustard Agents H, HD, and HT*; Medical Services, **revised (draft) February 2003**.

New CDC

Federal Register, vol. 68, No. 196, pp. 58348-58351 *(nerve agents)*, **October 9, 2003**.

Federal Register, vol. 69, No. 85, pp24164-24168 (*sulfur mustard*), **3 May 2004**

NA = not previously developed.

Table F-2. Acute Exposure Guidelines Levels (mg/m^3) for Nerve Agents and Sulfur Mustard (NRC/COT, 2003)

Agent	AEGL	10 min	30 min	1 hr	4 hr	8 hr
GA	1	0.0069	0.0040	0.0028	0.0014	0.0010
GB	1	0.0069	0.004	0.0028	0.0014	0.0010
GD	1	0.0035	0.002	0.0014	0.0007	0.0005
GF	1	0.0035	0.002	0.0014	0.0007	0.0005
VX	1	0.00057	0.00033	0.00017	0.00010	0.000071
HD	1	0.40	0.13	0.067	0.017	0.008
GA	2	0.087	0.05	0.035	0.017	0.0013
GB	2	0.087	0.05	0.035	0.017	0.0013
GD	2	0.044	0.025	0.018	0.0085	0.0065
GF	2	0.044	0.025	0.018	0.0085	0.0065
VX	2	0.0072	0.0042	0.0029	0.0015	0.0010
HD	2	0.60	0.20	0.10	0.025	0.013
GA	3	0.76	0.38	0.26	0.14	0.10
GB	3	0.38	0.19	0.13	0.070	0.051
GD	3	0.38	0.19	0.13	0.070	0.051
GF	3	0.38	0.19	0.13	0.070	0.051
VX	3	0.029	0.015	0.010	0.0052	0.0038
HD	3	3.9	2.7	2.1	0.53	0.27

APPENDIX G
HAZARD SEVERITY RANGES AND ASSOCIATED TOXICITY CRITERIA

* The color coded tables reflect the hazard severity described in Table 5-1 of this and the agent-specific *Ct* estimates described in Appendix C of this report.

Currently:

- Green: Negligible hazard severity range.
- Yellow: Marginal severity range.
- Orange: Critical hazards severity range.
- Red: Catastrophic severity range.
- PTE: population threshold estimate (as described in report).

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Table G.1 Hazard Severity Ranges for Inhalation/Ocular Exposures to Nerve Agents

(***Caveat***: The following table is a generalized representation of toxicity ranges and should not be used to determine exact *Ct* values. User is referred to Appendix E, Table E-4)

mg-min/m^3	GA Inhalation/Ocular Effects			GB Inhalation/Ocular Effects			GD Inhalation/Ocular Effects			GF Inhalation/Ocular Effects			VX Inhalation/Ocular Effects		
110															
	LCt99														
100															
	LCt84	ECt99sev													
	LCt50														
		ECt84sev													
	LCt16			LCt99			LCt99			LCt99					
50	LCt01	ECt50sev								LCt84	ECt99sev				
		ECt16sev		LCt84	ECt99sev		LCt84	ECt99sev		LCt50			LCt99		
				LCt50	ECt84sev		LCt50	ECt84sev			ECt84sev				
25		ECt01sev		LCt16			LCt16			LCt16					
				LCt01	ECt50sev		LCt01	ECt50sev		LCt01	ECt50sev		LCt84	ECt99sev	
					ECt16sev			ECt16sev			ECt16sev		LCt50		
					ECt01sev			ECt01sev			ECt01sev		LCt16	ECt84sev	
10														ECt50sev	
														ECt16sev	
5													LCt01		
			ECt99mild			ECt99mild								ECt01sev	
			ECt84mild			ECt84mild									
1			ECt50mild			ECt50mild			ECt99mild			ECt99mild			
			ECt16mild			ECt16mild			ECt84mild			ECt84mild			
0.5															
			ECt01mild			ECt01mild			ECt50mild			ECt50mild			ECt99mild
									ECt16mild			ECt16mild			ECt84mild
0.1									ECt01mild			ECt01mild			ECt50mild
			PTE			PTE									ECt16mild
0.01									PTE			PTE			ECt01mild
															PTE
0.001															

PTE = Population Threshold Estimate, incorporates uncertainty factors to address most susceptible groups within military population, see Sections 4.2, 4.5 and Table 4.4

Table G-2. Hazard Severity Ranges for Inhalation/Ocular Exposures to Sulfur Mustard

(***Caveat***: The following table is a generalized representation of toxicity ranges and should not be used to determine exact *Ct* values. User is referred to Appendix E, Table E-4 for agent-specific *Ct* values)

mg-min/m^3	HD Inhalation/Ocular Effects		
2000	LCt99		
1500			
	LCt84		
1000	LCt50		
500	LCt16	ECt99sev	
300	LCt01		
200		ECt84sev	
			ECt99mild
100		ECt50sev	
50			ECt84mild
		ECt16sev	
20			ECt50mild
		ECt01sev	
10			ECt16mild
			ECt01mild
1			PTE

PTE = Population Threshold Estimate, incorporates uncertainty factors to address most susceptible groups within military population, see Sections 4.2, 4.5, 4.6,. 4.7 and Table 4.4

Table G-3. Hazard Severity Ranges for Percutaneous Vapor* Exposures

(***Caveat***: The following table is a generalized representation of toxicity ranges and should not be used to determine exact *CT* values. User is referred to Appendix E, Table E-8 for agent-specific *Ct* values. *Note: These represent Percutaneous Vapor Exposure only. If inhalation/ocular exposure occurs, toxic effects occur at much lower levels (see effects gradient for inhalation/ocular effects.

mg-min/m^3	GA Percutaneous Vapor Effects			GB Percutaneous Vapor Effects			GD Percutaneous Vapor Effects			VX Percutaneous Vapor Effects			HD Percutaneous Vapor Effects (warm-hot climate)		
50,000															
	LCt99														
40,000															
		ECt99sev		LCt99											
	LCt84				ECt99sev										
20,000		ECt84sev		LCt84									LCt99		
	LCt50														
		ECt50sev		LCt50	ECt84sev								LCt84		
10,000													LCt50		
	LCt16	ECt16sev		LCt16	ECt50sev		LCt99						LCt16		
5,000	LCt01		ECt99mild		ECt16sev										
		ECt01sev		LCt01			LCt84	ECt99sev					LCt01		
			ECt84mild			ECt99mild	LCt50								
2,500					ECt01sev			ECt84sev							
			ECt50mild				LCt16	ECt50sev							
						ECt84mild									
			ECt16mild			ECt50mild	LCt01	ECt16sev						ECt99sev	
1,000															
			ECt01mild			ECt16mild		ECt01sev	ECt99mild						
500															
			PTE			ECt01mild			ECt84mild	LCt99				ECt84sev	
									ECt50mild	LCt84					
						PTE			ECt16mild					ECt50sev	
100									ECt01mild	LCt50					
										LCt16				ECt16sev	ECt99mild
50										LCt01	ECt99sev			ECt01sev	ECt84mild
									PTE		ECt84				
20											ECt50sev	ECt99mild			ECt50mild
											ECt16sev	ECt84mild			
10											ECt01sev	ECt50mild			ECt16mild
												ECt16mild			
												ECt01mild			ECt01mild
												PTE			PTE
1															

PTE = population threshold estimate; address variability in population susceptibility; see section 4.6.2.2 and Table 4-8

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GLOSSARY

acute effect - an effect that occurs or develops rapidly after a single exposure to a substance (adapted from Klaassen, 2001)

acute exposure - single or multiple exposure(s) to a substance over a period of less than 24 hours (adapted from USACHPPM, 2001).

AEGL - Acute Exposure Guideline Level; concentrations of a chemical in air above which different types of health effects could begin to occur in unprotected civilian populations after single, one-time exposures lasting minutes to hours (See Section 4.3.3)

AEL – airborne exposure limit (see Section 4.3.3).

anemia - a condition in which the blood is deficient in red blood cells, in hemoglobin, or in total volume, resulting in insufficient oxygen to tissues and organs (adapted from Merriam Webster 1995; University of Newcastle upon Tyne, 1997-2003).

anticholinesterase (AChE) - a chemical, such as an organophosphate, that blocks nerve impulses by inhibiting the activity of the enzyme cholinesterase (adapted from University of Newcastle upon Tyne, 1997-2003).

apoptosis - programmed cell death in normally functioning human and animal cells that occurs naturally when age or state of cell health and condition dictates (adapted from University of Newcastle upon Tyne, 1997-2003).

ataxia - an inability to coordinate voluntary muscular movements; symptomatic of some nervous disorders (Merriam Webster, 1995).

Bronchoconstriction - narrowing of the air passages of the lungs, typically as a result of bronchial smooth muscle contraction (Saunders, 2002)

Bronchopneumonia - pneumonia involving many relatively small areas of lung tissue (Merriam Webster, 1995).

CDC – Centers for Disease Control and Prevention.

CENTCOM – U.S. Army Central Command.

cholinesterase (ChE) - an enzyme that breaks down the neurotransmitter acetylcholine to stop its action. It is found in the blood, liver, pancreas as well as other organs and tissues. (University of Newcastle upon Tyne ,1997-2003; BioTech Resources, 1995-1998)

clinical effect - a sign of a condition that can be observed or measured by a medically trained professional in an animal or human (e.g., elevated pulse) (adapted from Merriam Webster, 1995, Rothenberg, 1992, University of Newcastle upon Tyne, 1997-2003).

concentration - the total quantity of a substance present in a given volume of a gas or liquid. It may be expressed in either of two ways: 1) as a unit of mass per unit of volume, such as milligrams per cubic meter (mg/m^3) or grams per liter (gm/L), or 2) as volume per volume, such as parts per million (ppm). (adapted from USACHPPM, 2001).

conjunctival congestion - an excessive accumulation of blood in the mucous membrane that lines the inner surface of the eyelids and is continued over the fore part of the eyeball (Merriam Webster, 1995).

conjunctivitis - inflammation of the mucous membrane that lines the inner surface of the eyelids and is continued over the forepart of the eyeball (Merriam Webster, 1995).

COT - Committee on Toxicology (of the National Research Council).

CSEPP – Chemical Stockpile Emergency Preparedness Program.

cutaneous - of, relating to, or affecting the skin (Merriam Webster, 1995).

CWA—chemical warfare agent.

DA – Department of the Army.

DA Pam – Department of the Army Pamphlet.

DATSD-CBD - Deputy Assistant to The Secretary of Defense Chemical and Biological (Warfare Agent) Defense.

detoxification - reduction of the toxic properties of a substance by chemical changes induced in the body, producing a compound which is less poisonous or is more readily eliminated (definition of "metabolic detoxification" in Saunders, 2002).

delayed effect - a local or generalized response occurring after a lapse of time following a single administration of a substance. The elapsed time may be hours, days, or years after exposure to a toxic substance; as opposed to an "acute effect." (adapted from Klaassen 2001; University of Newcastle upon Tyne, 1997-2003).

distal neuropathy - a functional disturbance and/or pathological change in the nerves of the extremities (e.g., hands or feet) (adapted from Merriam Webster 1995; University of Newcastle upon Tyne, 1997-2003).

DOD – Department of Defense.

dosage – (1) the amount of substance administered (or received) per body weight, and often expressed in units of mg/kg. (adapted from Klaassen, 2001; USACHPPM, 2001); (2) a modeling estimate incorporating the integration of concentration, C, in mg/m^3 and time, t, in minutes, and also referred to as Ct (units of $mg\text{-}min/m^3$). The Ct is a mathematical concept that is a useful exposure index to vapors and small aerosols that can be absorbed by inhalation. When the Ct is multiplied by a breathing rate and retention efficiency, the result is considered by modelers to characterize an inhaled "dose" (adapted from IEM 1994). (Please NOTE that authoritative sources consider Ct ($mg\text{-}min/m^3$) to represent cumulative exposure only, and not an estimate of absorbed material.)

dose - the amount of agent or energy that is taken into or absorbed by the body; the amount of substance, radiation, or energy absorbed in a unit volume, an organ, or an individual. Common units of dose include mg/animal, mg/man (USACHPPM, 2001).

dyspnea - difficult or labored respiration; shortness of breath (Merriam Webster 1995; Rothenberg 1992).

Echelon Levels of Care/Preventive Medicine Support—

- Echelon I: Care that is provided by an individual (such as, self-aid, buddy aid, combat lifesaver, or combat medic) or by medical personnel in a treatment squad. Care includes immediate lifesaving measures; disease and non-battle injury prevention; combat stress control prevention; and patient collection and evacuation to next level of care.

- Echelon II: Care that duplicates and expands upon Level I; includes resuscitative care; and expands available services by adding dental, laboratory, x-ray, and patient holding capabilities. Level II includes patient evacuation from Level I and is usually provided by divisions, separate brigades, and armored cavalry regiments; provides medical threat assessment; training and technical support to field sanitation teams; medical surveillance for selected diseases; and surveys, inspections, and risk management activities at Level II.

- Level III: Care that duplicates and expands upon Level II; includes emergency surgical services with supporting medical treatment facility (such as, Forward Surgical Team and Combat Support Hospital); and patient regulating and evacuation. A variety of preventive medicine detachments; sections; elements; and augmentation assets provide a much broader scope of preventive medicine activities at Level III and Level IV.

- Level IV: Care that is provided in a field hospital or general hospital staffed and equipped for general and specialized medical and surgical care. Services include rehabilitative care for return-to-duty within the theater evacuation policy and patient regulating and evacuation.

- Level V: Care is provided at continental U.S. fixed facility hospitals staffed and equipped for the most definitive care available within the Army Medical Department health system.

EC_{50} – effective concentration; the concentration causing a specifically defined effect in 50 percent of the given population.

ECt – exposure concentration.

ECt_{50} – median exposure concentration. The dosage causing a specifically defined effect in 50 percent of the given population. The route of exposure can be either inhalation or percutaneous (USACHPPM, 2001).

edema - excessive accumulation of fluid in the tissues, thus causing swelling (Rothenberg, 1992).

EEG – electroencephalogram; tracing of brain waves produced by an encephalograph (an apparatus for detecting and recording brain waves) (Merriam Webster, 1995).

endpoint - a detectable and quantitative biological response; often used to describe results in a laboratory experiment of dose-response and to illustrate response mechanisms. The biological endpoint may be observed through changes in cell culture, tissues, laboratory animals, etc. and is not necessarily adverse (e.g., change in blood enzyme activity). (Adapted from USACHPPM, 2001; University of Newcastle upon Tyne, 1997-2003; Morris, 1992).

epithelial lining (of the airway) - the membrane of cells lining the respiratory tract (adapted from Rothenberg 1992 definition of "epithelium").

erythema - abnormal redness and inflammation of the skin caused by congestion and dilation (widening) of the capillaries (tiny blood vessels) and which may be due to various causes such as chemical poisoning or sunburn; usually localized or patchy. (adapted from Morris, 1992; USACHPPM, 2001)

exposure - the amount of chemical that enters the body by some route (inhalation, direct eye or skin contact, or ingestion) for a specified frequency and duration (USACHPPM, 2001).

fasciculation - small, local, muscular twitching, visible through the skin and involving simultaneous contraction of adjacent groups of muscle fibers (adapted from Merriam Webster 1995; University of Newcastle upon Tyne, 1997-2003).

FEMA – Federal Emergency Management Agency.

FHP - Force Health Protection. A unified and comprehensive strategy that aggressively promotes a health and fit force and provides full protection from all potential health hazards throughout the deployment process. It includes health and fit- force promotion, casualty and injury prevention, and casualty care management (DA, AR 40-5 (draft), *Army Preventive Medicine).*

GPL – general population limit.

HAZMAT - hazardous materials.

HD – sulfur mustard.

heterogeneous population - a group of people with diverse physical and physiological characteristics (as age, gender, race, ethnicity, body weight, physical conditioning, health status, etc.); the 'general population' is a term historically used as an example of a heterogenous population; also referred to as a **mixed population**.

heterozygous - containing different forms of a particular gene, one inherited from each parent; hybrid (offspring of two genetically different parents and thus representing a heterogeneous genetic complement)(adapted from Morris, 1992; University of Newcastle upon Tyne, 1997-2003).

histopathology - the study of microscopic changes in diseased tissues (University of Newcastle upon Tyne, 1997-2003).

Homeland Security – a national strategy to strengthen protections against threats or attacks within the U.S. (USACHPPM, 2001).

homozygous - the antithesis of heterozygous; possessing two identical forms of a particular gene, one inherited from each parent (adapted from Rothenberg 1992; University of Newcastle upon Tyne 1997-2003; Morris, 1992).

hydrolyze - the act of splitting a compound into fragments by the addition of water, the hydroxyl (OH^-) group being incorporated in one fragment and the hydrogen atom (H^+) in the other (University of Newcastle upon Tyne, 1997-2003).

IDA - Institute for Defense Analysis.

IDLH – immediately dangerous to life and health.

Immunosuppression - suppression (as by cancer-treatment drugs) of natural immune responses, thereby rendering the individual susceptible to many common infections (adapted from Merriam Webster, 1995).

incapacitating effect - an effect that renders an individual unable to perform normal activities or tasks. When untreated and/or in the absence of decontamination, some incapacitating effects can progress to the point of lethality (adapted from USACHPPM, 2001).

Interspecies - existing, occurring, or arising between species; involving members of different species (adapted from Merriam Webster, 2003).

Intraspecies - arising or occurring within a species; involving the members of one species (Lexico Publishing Group, LLC, 2003).

IPE - individual protective equipment.

JCS - Joint Chiefs of Staff.

JP – Joint Publication.

keratitis - inflammation of the cornea of the eye characterized by burning or smarting, blurring of vision, and sensitiveness to light (Merriam Webster, 1995).

kg – kilogram.

latent effect - an effect that may become evident at some delayed time post-exposure, and may be a consequence of injury that requires a period of time to develop before it is visible or can be measured (adapted from Merriam Webster, 1995; Morris, 1992).

LC – lethal concentration.

LCt_{50} – lethal concentration multiplied by time for 50 percent population effect.

LD – lethal dose.

LD_{50} – a dosage of a substance that produces death in 50 percent of the exposed population usually as a single dose, with the route of exposure specified (USACHPPM, 2001).

leucopenia - a condition in which the number of circulating white blood cells is abnormally low and which is most commonly caused by a decreased production of new cells due to an infectious disease, as a reaction to various drugs or other chemicals, or in response to irradiation (adapted from Merriam Webster, 1995; Rothenberg, 1992).

LOAEL – lowest-observed adverse effect level.

local effect - an effect that occurs at the site of bodily contact (e.g., eyes, skin) with a substance or condition (as a skin burn) (adapted from USACHPPM, 2001).

log-probit analysis - a method of extrapolating estimated threshold exposure levels from known median effects levels that assumes: (1) that each individual has a personal threshold exposure level, below which no effect occurs and above which effects are produced by exposure to a chemical; and (2) these threshold exposure levels are normally distributed in the population and can, thus, be estimated using statistical methods.

long-lasting effect - an effect that continues to be observed or measured for a period of time (perhaps days to multiple weeks) after the cause which first gave rise to it is removed (adapted from definition of "persistency" in University of Newcastle upon Tyne, 1997-2003). A long-lasting effect may be of no clinical significance and reversible with sufficient time.

low-level - those exposures that do not produce health effects of significant physiological impact and, thus, will not pose notable operational (mission) impact. This involves a range of exposures and points along a chemical's dose-response continuum to include potential for mild non-impairing, minimally noticeable reversible acute effects and, for certain chemicals, possibility of delayed and/or non-clinical effects (reversible or non-reversible), as well as levels associated with no anticipated effects of any kind.

median effect level - the dose of a substance or concentration of a substance in air that will produce a specified level of effect in 50 percent of the people exposed (e.g., LD_{50}, ECt_{50} threshold).

MEGs - military exposure guidelines; exposure guidelines documented in the USACHPPM TG 230 for assessing and characterizing chemical exposure risks according to ORM terminology.

m^2 – square meter.

µg – microgram.

µg/cm^2 – microgram per square centimeter.

µg/kg – microgram per kilometer.

mg/m^2 – milligram per square meter.

mg/m^3 – milligram per cubic meter.

mg-min/m^3 – milligram-minute per cubic meter.

minute volume - the quantity of gas expelled from the lungs per minute (Saunders, 2002).

mixed population - see **heterogeneous population**.

miosis - greater than normal contraction of the pupil of the eye, resulting in a reduced pupil diameter; transient and reversible effect; may be present in one or both eyes (adapted from USACHPPM, 2001; Merriam Webster, 1995).

MOPP - mission-oriented protective posture. A military term for individual protective equipment that includes suit, boots, gloves, mask with hood, as well as first-aid treatments and decontamination kits that are issues to soldiers (see JP 1-02). There are several levels of protectiveness offered by the types of protective clothing actually worn. For example, at MOPP 4, the full ensemble (over-garment suit, boots, mask and hood, and gloves) are all worn and closed (see Table 1-C, USACHPPM, 2002).

NBC - nuclear, biological and chemical (warfare).

neoplasm - a new growth of tissue serving no physiological function; tumor (Merriam Webster, 1995).

neuropathy - functional disturbance and/or pathological change in the nervous system (adapted from University of Newcastle upon Tyne, 1997-2003).

neurotoxic - toxic to nerves or nervous tissue (Merriam Webster, 1995).

NOAEL – no-observed adverse effect level.

non-clinical effect - an effect that is not sufficiently pronounced to be detected by a medically trained professional, possibly because the level of exposure was very mild or because the effect is in an early stage of development; also referred to as "subclinical." (adapted from University of Newcastle upon Tyne, 1997-2003).

normal distribution - also called Gaussian or parametric distribution. If each data point from a study is plotted on a graph and a single "bell-shaped" curve is formed as the average (or mean) value, the data are said to be normally distributed. If two or more "bell-shaped" curves are formed by the data plots, the data are said to be abnormally or nonparametrically distributed (adapted from Armitage and Berry, 1994).

NRC - National Research Council

OEH - occupational and environmental health.

OP – organophosphate.

OPIDN - organophosphate induced delayed neuropathy.

OPTEMPO - operational temp; the pace of an operation or operations; includes all the activities a unit is conducting; can be a single activity or series of operations (DA, 1998 (FM 100-14)).

ORM - operational risk management.

paraoxonase - an enzyme associated with high-density lipoprotein (HDL) that is present in the liver as well as other tissues and blood, and resistant to inhibition by organophosphate pesticides and nerve agents (Derelanko and Hollinger, 1995).

PB - pyridostigmine bromide.

permanent effect - a condition or state that cannot be remedied and which continues to exist without fundamental or marked change; irreversible (adapted from Rothenberg 1992; University of Newcastle upon Tyne, 1997-2003).

population threshold estimate (PTE) - the level at which members of the exposed population will first begin to demonstrate initial effects. Such an estimate must include consideration of those members of diverse population which may include more susceptible persons who would the first expected to be to have effects.

2-PAM chloride - protopam chloride, a nerve agent antidote.

PPE - personal protective equipment.

probit - a mathematical transformation method used to linearize percentile data obtained from lethality or effective dose studies. The probit of the percent responding in the study is linearly related to the dose, providing the data are normally distributed. In probit analyses, 50 percent effect is equal to 5.0 probit units. Because 0 percent and 100 percent effects are equal to infinity in this type of calculation, they are not used in probit analyses (adapted from Armitage and Berry, 1994).

PTE - population threshold estimate.

pupillary muscles - muscles that control the diameter of the pupil of the eye in response to the intensity of light (adapted from Merriam Webster, 1995).

RBC-ChE - red blood cell cholinesterase.

RfC – reference concentration.

RfD – reference dose.

rhinorrhea - a “running” nose; excessive mucous secretion from the nose (Merriam Webster 1995; Rothenberg 1992).

SFEMG - single fibre electromyographic; of or relating to a test which measures the response of a single muscle fiber to nerve stimulation (adapted from University of Newcastle upon Tyne, 1997-2003).

STEL – short-term exposure limit.

susceptibility factor - a characteristic that results in vulnerability to a specific toxic substance or pathogen, and thus increases one's likelihood of suffering injury or disease when exposed to that specific material (adapted from Merriam Webster, 1995; Morris 1992).

systemic effect - an effect that occurs when bodily systems (such as the circulatory or respiratory system) absorb a toxicant (which has contacted or entered the body) and transport the toxicant to one or more organs where effects are produced. Most substances that produce systemic toxicity do not cause a similar degree of toxicity in all organs, but usually demonstrate a major toxicity to one or a few organs. These are referred to as "target organs of toxicity" for that substance (adapted from USACHPPM, 2001).

threshold – the point at which a physiological effect begins to be produced.

TIC - toxic industrial chemical.

TTCP – The Technical Cooperation Program.

TWA – time-weighted average.

UF – uncertainty factor, a quantitative value applied to a data-derived concentration or dose estimate of a specific human health effect threshold to account for biological/physiological factors not addressed by the data set or its study design; UFs of 10 or 3 are often used as the default value to divide (lower) the data-derived estimate.

USACHPPM – U.S. Army Center for Health Promotion and Preventive Medicine.

USEPA – U.S. Environmental Protection Agency.

vesicant - a chemical warfare agent such as sulfur mustard (HD) or Lewisite (L) that induces blistering (vesicles) and tissue damage (FEMA/Army, 1996/1997).

WPL – worker population limit.

SOURCES:

Armitage, P. and G. Berry. 1994. *Statistical Methods in Medical Research.* Blackwell Scientific Publications, London.

BioTech Resources and Indiana University 1995-1998. *BioTech Life Science Dictionary,* http://biotech.icmb.utexas.edu/search/dict-search.html (accessed 3 April 2003).

Derelanko, M.J. and M. A. Hollinger (eds). 1995. *CRC Handbook of Toxicology.* CRC Press, Boca Raton, FL.

Department of the Army (DA). 1998. Field Manual (FM) 100-14, *Risk Management*, April 1998.

Department of the Army (DA). 2004 (Draft). Army Regulation (AR) 40-5, *Army Preventive Medicine (Draft).*

Federal Emergency Management Agency (FEMA) and U.S. Department of the Army 1996/1997. *Planning Guidance for the Chemical Stockpile Emergency Preparedness Program.*

Innovative Emergency Management (IEM) 1994. *Chemical Stockpile Emergency Preparedness Program (CSEPP) Glossary,* Baton Rouge, LA.

Joint Publication (JP) 1-02, *DOD Dictionary of Military and Associated Terms*. As amended through 23 March 2004.

Klaassen, C. D. (ed). 2001. *Casarett and Doull's Toxicology: The Science of Poisons*, 6th Ed. Mc-Graw Hill, Medical Publishing Division, New York, NY.

Lexico Publishing Group, LLC 2003. *Dictionary.com,* http://dictionary.reference.com/ (accessed 20 March 2003).

Merriam Webster, Inc., 1995. *Merriam Webster's Medical Dictionary,* Springfield, MA.

Merriam Webster, Inc. 2003. *Merriam Webster's Unabridged Online Dictionary*, 10th Ed., http://www.m-w.com/cgi-bin/dictionary?book=Dictionary, accessed 20 March 2003.

Morris, C. (ed). 1992. *Academic Press Dictionary of Science and Technology.* Academic Press, Harcourt Brace Jovanovich Publishers, San Diego, CA.

Rothenberg, R.E. 1992. *The New American Medical Dictionary and Health Manual,* Signet, New York, NY.

Saunders, W. B., Harcourt Health Services 2002. *Dorland's Illustrated Medical Dictionary,*http://www.mercksource.com/pp/us/cns/cns_health_library_frame. (accessed 20 March 2003).

University of Newcastle upon Tyne, Department of Medical Oncology 1997-2003, "On-Line Medical Dictionary," http://cancerweb.ncl.ac.uk/omd/, accessed 26 Feb 2003.

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Technical Guide 204. 2001. *Glossary of Terms for Nuclear, Biological, and Chemical Agents and Defense Equipment*. http://chppm-www.apgea.army.mil/documents/TG/TECHGUID/TG204a.pdf

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Technical Guide 244. 2002. *The Medical NBC Battlebook*.